

**Confidential Treatment Requested by Prelude Therapeutics Incorporated
Pursuant To 17 C.F.R. Section 200.83**

As confidentially submitted to the Securities and Exchange Commission on December 21, 2020
This draft registration statement has not been publicly filed with the Securities and Exchange Commission and all information herein remains confidential.
Registration No.

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**
Washington, D.C. 20549

**FORM S-1
REGISTRATION STATEMENT**

*Under
The Securities Act of 1933*

PRELUDE THERAPEUTICS INCORPORATED

(Exact name of Registrant as specified in its charter)

Delaware
(State of incorporation or
organization)

2834
(Primary Standard Industrial
Classification Code Number)

81-1384762
(I.R.S. Employer
Identification Number)

200 Powder Mill Road
Wilmington, Delaware 19803
(302) 467-1280

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Kris Vaddi, Ph.D.
Chief Executive Officer
Prelude Therapeutics Incorporated
200 Powder Mill Road
Wilmington, Delaware 19803
(302) 467-1280

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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**Approximate date of commencement of proposed sale to the public:
As soon as practicable after the effective date of this registration statement.**

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933 check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer" "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer Accelerated filer
Non-accelerated filer Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Proposed Maximum Aggregate Offering Price(1)(2)	Amount of Registration Fee
Common Stock, par value \$0.0001 per share	\$	\$

(1) The proposed maximum aggregate offering price includes the offering price of additional shares that the underwriters have the option to purchase.

(2) Estimated solely for purposes of calculating the registration fee in accordance with Rule 457(o) under the Securities Act of 1933, as amended.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities, and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

**SUBJECT TO COMPLETION, DATED _____, 2021
PRELIMINARY PROSPECTUS**

Shares



Common Stock

We are offering _____ shares of our common stock.

Our common stock is listed on The Nasdaq Global Select Market under the symbol “PRLD”. The closing price of our common stock on _____, 2021, as reported by The Nasdaq Global Select Market, was \$ _____ per share.

We have two classes of common stock: the voting common stock and the non-voting common stock. For a description of the rights of the voting common stock and non-voting common stock, please see “Description of Capital Stock” beginning on page 178 of this prospectus. We are offering voting common stock in this offering, and unless otherwise noted, all references in this prospectus to our “common stock” refer to our voting common stock. The non-voting common stock is not listed for trading on any securities exchange.

We are an “emerging growth company” and “smaller reporting company” as defined under the U.S. federal securities laws and will be subject to reduced public company reporting requirements for this prospectus and future filings. See “Prospectus Summary—Implications of Being an Emerging Growth Company and a Smaller Reporting Company.”

Investing in our common stock involves a high degree of risk. Please read “[Risk Factors](#)” beginning on page 12 of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	<u>PER SHARE OF COMMON STOCK</u>	<u>TOTAL</u>
Public offering price	\$ _____	\$ _____
Underwriting discounts and commissions(1)	\$ _____	\$ _____
Proceeds, before expenses, to us	\$ _____	\$ _____

(1) See “Underwriters” for a description of all compensation payable to the underwriters.

We have granted the underwriters an option for a period of 30 days from the date of this prospectus to purchase an additional _____ shares of common stock.

The underwriters expect to deliver the shares of common stock against payment in New York, New York on or about _____, 2021.

MORGAN STANLEY

GOLDMAN SACHS & CO. LLC

BofA SECURITIES

Prospectus dated _____, 2021

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Neither we nor the underwriters have authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus or in any applicable free writing prospectus is current only as of its date, regardless of its time of delivery or any sale of shares of our common stock.

For investors outside of the United States: We have not, and the underwriters have not, done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the United States. Persons outside of the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus outside of the United States.

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TRADEMARKS

The mark “Prelude Therapeutics,” the Prelude logo and all product names are our common law trademarks. All other service marks, trademarks and trade names appearing in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and tradenames referred to in this prospectus appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

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PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our common stock, you should carefully read this entire prospectus, including our financial statements and the related notes thereto and the information set forth under the sections entitled “Risk Factors,” “Selected Financial Data” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” in each case included in this prospectus. Some of the statements in this prospectus constitute forward-looking statements that involve risks and uncertainties. See the section entitled “Special Note Regarding Forward-Looking Statements.” Unless the context otherwise requires, we use the terms “Prelude,” “the company,” “we,” “us” and “our” in this prospectus to refer to Prelude Therapeutics Incorporated.

Overview

We are a clinical-stage precision oncology company focused on discovering and developing small molecule therapies optimized to target the key driver mechanisms in cancers with high unmet need. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our target class- and technology platform-agnostic approach, we have built an efficient, fully-integrated drug discovery engine to identify compelling biological targets and create new chemical entities, or NCEs, that we rapidly advance into clinical development. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our rapid progress in creating a wholly-owned, internally developed pipeline. Since our inception in 2016, we have received clearance from the U.S. Food and Drug Administration, or the FDA, for three investigational new drug applications, or INDs, and successfully advanced these three programs into clinical development. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development beginning in 2021.

By focusing on developing agents using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of six distinct programs spanning methyltransferases, kinases, protein-protein interactions and targeted protein degraders. Our pipeline is geared towards serving patients with high unmet medical need where there are limited or no treatment options. We are exploring therapies in both solid tumors and hematological malignancies such as adenoid cystic carcinoma, or ACC, homologous recombination deficient positive, or HRD+, cancers, myelofibrosis, or MF, and glioblastoma multiforme, or GBM, amongst others. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

Our lead product candidates are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. The potency and selectivity of our product candidates is supported by preclinical data demonstrating nanomolar inhibition of PRMT5 and no inhibition of related enzymes at 1,000 times higher concentration of our product candidates. We are currently advancing our first clinical candidate, PRT543, in a Phase 1 clinical trial in select solid tumors and myeloid malignancies in patients who are refractory to or intolerant of established therapies. Interim Phase 1 results indicate dose-dependent increases in exposure and target engagement, and we have observed early signs of clinical activity, including an ongoing, confirmed complete response, or CR, in a patient with HRD+ high grade serous ovarian cancer through nine months of therapy. A complete response is defined as the disappearance of all target lesions. While we will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by the FDA or other regulatory authorities, and while such approval is not guaranteed, we are encouraged by the clinical activity as of the date of this prospectus. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

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We are also advancing PRT811, a second PRMT5 inhibitor that we have optimized for high brain exposure, in a Phase 1 clinical trial in solid tumors, including GBM. As of the date of this prospectus, the trial has demonstrated early signs of clinical activity and tolerability. The previously disclosed refractory GBM patient whose tumor had demonstrated a 66% reduction on monotherapy PRT811 subsequently underwent a follow-up MRI at week 18 and the regression has improved to 77% from baseline, confirming a partial response, or PR, per RANO (response assessment in neuro-oncology) criteria. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the first half of 2021 and anticipate obtaining initial clinical data from these expansion cohorts by the end of 2021.

PRT1419, our third clinical candidate, is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. The potency and selectivity of PRT1419 is supported by preclinical data demonstrating nanomolar inhibition of MCL1 and no inhibition of related enzymes at 200 times higher concentration of our product candidate. We have begun enrolling patients with hematologic malignancies, including patients with myelodysplastic syndrome, or MDS, acute myeloid leukemia, or AML, non-Hodgkin’s lymphoma, or NHL, and multiple myeloma, or MM, into the Phase 1 clinical trial for PRT1419. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the second half of 2021.

Our pipeline is summarized in the figure below:



* Currently in Phase 1 dose escalation

Prelude Discovery and Development Approach

We carefully evaluate and select our targets based on three key pillars, which provide a framework for optimizing our drug discovery and development efforts.

- Identify target mechanisms with compelling biological rationale
 - *Current target mechanisms of focus include: transcriptional regulation, deoxyribonucleic acid, or DNA, repair pathway, cell cycle regulation, exploitation of synthetic lethality and brain penetrant molecules*
- Leverage our advanced medicinal chemistry capabilities to create better product candidates
 - *We view all target classes equally and strive to invent clinical candidates that meet our desired target product profiles*

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- Pursue targets that drive cancers with high unmet need
 - *Focus on targets that allow us to select patients and cancers with high unmet need with no approved therapies, or patient populations that are underserved by approved treatments*

Once we have identified optimal targets using the three pillars above, we engage our unique discovery engine to rapidly and efficiently invent and develop molecules. We believe our expertise, capabilities and experience to select high value biological targets and invent molecules with an optimized balance of biological and chemical properties differentiates us from others in the precision oncology space. We believe our unique discovery engine will enable us to continue delivering a new IND every 12 to 18 months.

We design our clinical trials to leverage the broad utility of our compounds with a focus on efficient regulatory pathways to enable our potentially transformative medicines to quickly reach patients with high unmet medical need. By focusing on validated cancer signaling pathways and early clinical proof-of-concept, we seek to advance our programs through expedited approval processes.

Our Product Candidates

Our first two candidates, PRT543 and PRT811, are designed to be potent, selective and oral inhibitors of PRMT5. We believe targeting PRMT5 has broad applicability and a strong scientific rationale for the treatment of cancer as it regulates transcription, translation and messenger ribonucleic acid, or mRNA, as well as the splicing of cancer related genes. Inhibition of PRMT5 has been observed to suppress tumor growth and produce synthetic lethality preclinically.

PRT543, our first clinical candidate, is currently in a Phase 1 clinical trial in advanced solid tumors and select myeloid malignancies. We have been encouraged by both the clinical activity and tolerability data that have been seen in 61 patients (42 with advanced solid tumors, one with NHL, 11 with MF and seven with MDS) that have enrolled into the study as of December 16, 2020. We have observed early signs of clinical activity, including a confirmed CR per RECIST v1.1, in a patient with HRD+ high grade serous ovarian cancer, in the 35 mg 5x/week (once a day, for five days, with two days off) cohort. This patient has received nine months of study therapy as of December 16, 2020 and remains in CR. We will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by FDA or other regulatory authorities, and such approval is not guaranteed. In addition, extended duration of therapy and improvements in symptoms have been observed in several patients with MF, with one patient demonstrating a response of clinical improvement and another patient showing an approximately 66% reduction in Total Symptom Score, or TSS, a validated clinical endpoint in MF. Clinical improvement means an achievement in anemia, spleen, or symptom response without progressive disease or increase in the severity of anemia, thrombocytopenia or neutropenia. We have begun enrolling patients into the expansion portion of the Phase 1 clinical trial in select tumor types that are potentially driven by PRMT5 dysregulation. These tumor types include ACC, MF, genomically selected MDS and HRD+ tumors. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

PRT811, our second clinical candidate, is currently advancing in the dose escalation portion of a Phase 1 clinical trial in solid tumors, including GBM and primary central nervous system lymphomas, or PCNSL. PRT811 has been optimized for high brain exposure and hence we believe is uniquely positioned to treat PRMT5 sensitive CNS cancers. We have been encouraged by both the clinical activity and tolerability data that have been seen in 24 patients (eight with GBM, 16 with various advanced solid tumors) that have enrolled into the dose escalation portion of the study as of December 16, 2020. We have observed early signs of clinical activity in a

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refractory GBM patient whose tumor initially demonstrated a 66% reduction on monotherapy PRT811 at week 6, and subsequently underwent a follow-up MRI at week 18, and the regression has improved to 77% from baseline, confirming a PR per RANO (response assessment in neuro-oncology) criteria. This patient has received five months of study therapy as of December 16, 2020 and remains in PR and is clinically stable. We will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by FDA or other regulatory authorities, and such approval is not guaranteed. We plan to initially enroll patients in the expansion portion of the clinical trial with GBM, PCNSL and solid tumors with metastatic disease to the CNS once we have established an expansion dose. We expect these expansions to begin in the first half of 2021 and anticipate initial clinical results from these expansion cohorts by the end of 2021.

PRT1419, our third clinical candidate, is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. We believe hematological malignancies are particularly sensitive to MCL1 inhibitors. MCL1 upregulation has been noted as a mechanism of acquired resistance to venetoclax and tyrosine kinase inhibitors, or TKIs. In addition, certain solid tumors are responsive to MCL1 inhibition, informing a potential patient selection strategy. We have enrolled four patients into the Phase 1 clinical trial investigating oral PRT1419 in high risk MDS, AML, NHL and MM. Additionally, during the fourth quarter of 2020 we filed an IND with the FDA for an intravenous, or IV, formulation of PRT1419, which we plan to evaluate in various advanced solid tumors. We believe that the physicochemical and pharmacological properties of PRT1419 allow the optionality of administering PRT1419 by either oral or IV routes.

In addition to our three clinical stage candidates, our two most advanced preclinical programs target cyclin-dependent kinase 9, or CDK9, and Brahma homologue, or BRM, otherwise known as SMARCA2, respectively. PRT2527, designed to be a potent and selective CDK9 inhibitor, has entered IND-enabling studies with an IND submission expected in 2021. We have also identified SMARCA2 protein degraders that appear to be potent based on preclinical data demonstrating degradation of SMARCA2 at sub-nanomolar concentration. Optimization of the lead compound, PRT-SCA2, is progressing, and we expect to initiate IND-enabling studies in 2021. Our sixth program is exploring a kinase target for solid tumors. We are optimizing our lead compound, PRT-K4, and expect to begin IND-enabling studies in 2021.

Our Team

We were founded in 2016 by Kris Vaddi, Ph.D., a founding scientist at Incyte, and have assembled an experienced management team and board of directors with deep expertise in oncology and drug development. We have built from the “ground up” our internal discovery team, led by scientific and medical teams with deep expertise and proven capabilities in inventing and rapidly advancing small molecule medicines that address important gaps in the current precision oncology ecosystem. Members of our management team have successfully developed and commercialized numerous drugs such as Jakafi, Olumiant, Velcade, VITRAKVI, Retevmo, Tavegyl and Pemazyre.

Risks Factor Summary

Our business is subject to a number of risks, including risks that may prevent us from achieving our business objectives or may adversely affect our business, financial condition, results of operations, cash flows and prospects that you should consider before making a decision to invest in our common stock. These risks are discussed more fully in the section titled “Risk Factors” beginning on page 12 of this prospectus, and include the following:

- We have a limited operating history, which may make it difficult to evaluate the success of our business to date and to assess our future viability. We have incurred significant operating losses since our inception and have not generated any revenue. We expect to incur continued losses for the foreseeable future and may never achieve or maintain profitability.

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- Even if this offering is successful, we will require substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed or on terms acceptable to us, we could be forced to delay, reduce or eliminate our research or drug development programs or any future commercialization efforts or other operations.
- Raising additional capital may cause dilution to our stockholders, including purchasers of common stock in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.
- We are highly dependent on the success of our product candidates, PRT543, PRT811 and PRT1419, which are in early clinical development, and PRT2527, which is in preclinical development. We have not completed successful late-stage pivotal clinical trials or obtained regulatory approval for any product candidate. We may never obtain approval for any of our product candidates or achieve or sustain profitability.
- The development and commercialization of pharmaceutical products are subject to extensive regulation, and we may not obtain regulatory approvals for PRT543, PRT811, PRT1419, PRT2527 or any other product candidates, on a timely basis or at all.
- We rely, and intend to continue to rely, on third parties to conduct our clinical trials and perform some of our research and preclinical studies.
- We currently rely on third-party suppliers, including single source suppliers, to manufacture preclinical and clinical supplies of our product candidates and we intend to rely on third parties to produce commercial supplies of any approved product candidate.
- If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, third parties, including our competitors, could develop and commercialize products similar or identical to ours, and our ability to commercialize our product candidates successfully may be adversely affected.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.
- The COVID-19 pandemic could adversely impact our business, including our clinical trials and clinical trial operations.
- Delaware law and provisions in our restated certificate of incorporation and amended and restated bylaws could make a merger, tender offer, or proxy contest difficult, thereby depressing the market price of our common stock.
- The exclusive forum provision in our organizational documents may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims.

Corporate Information

We were incorporated under the laws of the State of Delaware in February 2016. Our principal executive offices are located at 200 Powder Mill Road, Wilmington, DE 19803, and our telephone number is (302) 467-1280. Our website address is www.preludetx.com. The information contained on, or that can be accessed through, our website is not part of, and is not incorporated by reference into, this prospectus. Investors should not rely on any such information in deciding whether to purchase our common stock.

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Implications of Being an Emerging Growth Company and a Smaller Reporting Company

As a company with less than \$1.07 billion in revenue during our last fiscal year, we qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act. An emerging growth company may take advantage of reduced reporting requirements that are otherwise applicable to public companies. These provisions include, but are not limited to:

- being permitted to present only two years of audited financial statements and only two years of related “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure in our periodic reports and registration statements, including this prospectus;
- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, on the effectiveness of our internal controls over financial reporting;
- reduced disclosure obligations regarding executive compensation arrangements in our periodic reports, proxy statements and registration statements, including this prospectus; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may use these provisions until December 31, 2025. However, if certain events occur prior to December 31, 2025, including if we become a “large accelerated filer,” our annual gross revenues exceed \$1.07 billion or we issue more than \$1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five-year period.

We have elected to take advantage of certain of the reduced disclosure obligations in the registration statement of which this prospectus is a part and may elect to take advantage of other reduced reporting requirements in future filings. As a result, the information that we provide to our stockholders may be different than you might receive from other public reporting companies in which you hold equity interests.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies.

We have elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest of (1) the last day of our first fiscal year (a) in which we have total annual gross revenues of at least \$1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30th, (2) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period and (3) December 31, 2025.

We are also a “smaller reporting company,” meaning that the market value of our stock held by non-affiliates plus the proposed aggregate amount of gross proceeds to us as a result of this offering is less than \$700.0 million and our annual revenue is less than \$100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company after this offering if either (i) the market value of our stock held by non-affiliates is less than \$250.0 million or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than

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\$700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

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THE OFFERING

Common stock offered by us	shares
Option to purchase additional shares	We have granted the underwriters an option, exercisable for 30 days after the date of this prospectus, to purchase up to an additional shares from us at the public offering price per share less the underwriting discounts and commissions.
Total common stock to be outstanding immediately after this offering	shares (or shares, if the underwriters exercise their option to purchase additional shares in full).
Use of proceeds	<p>We estimate that the net proceeds from this offering will be approximately \$ million (or approximately \$ million if the underwriters exercise their option to purchase additional shares in full), based upon the assumed public offering price of \$ per share, which was the last reported sale price of our common stock on the Nasdaq Global Select Market on , 2021, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.</p> <p>We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents, to advance the clinical development of PRT543, PRT811, PRT1419 and PRT2527 and to fund further development of our preclinical programs towards IND filings and/or into clinical trials and to fund working capital and general corporate purposes. See the section entitled “Use of Proceeds.”</p>
Voting rights	We have two classes of common stock: the voting common stock and non-voting common stock. For a description of the rights of the voting common stock and non-voting common stock, see “Description of Capital Stock.”
Risk factors	You should read the section entitled “Risk Factors” in this prospectus for a discussion of factors that you should consider carefully before deciding to invest in shares of our common stock.
Nasdaq Global Select Market symbol	“PRLD”

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The number of shares of our common stock and non-voting common stock to be outstanding after this offering is based on 43,703,381 shares of our common stock outstanding as of September 30, 2020 (including 1,312,024 unvested restricted shares outstanding as of September 30, 2020) and excludes:

- 6,649,882 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2020 under our 2016 Stock Incentive Plan, or the 2016 Plan, and our 2020 Equity Incentive Plan, or the 2020 Plan, with a weighted average exercise price of \$7.00 per share;
- 127,000 shares of common stock issuable upon the exercise of stock options granted after September 30, 2020 under the 2020 Plan with an exercise price of \$52.90; and
- 5,197,407 shares of common stock reserved for future issuance as of September 30, 2020 under our stock-based compensation plans, consisting of (i) 4,677,407 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 520,000 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan, or the ESPP. Our 2020 Plan and ESPP also provide for automatic annual increases in the number of shares reserved under the plans each year, as more fully described in “Executive Compensation—Equity Compensation Plans and Other Benefit Plans.”

Except as otherwise indicated, all information in this prospectus assumes or gives effect to:

- no exercise of outstanding options after September 30, 2020; and
- no exercise of the underwriters’ option to purchase additional shares of our common stock.

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SUMMARY FINANCIAL DATA

The following tables set forth our summary statements of operations and balance sheet data. The summary statement of operations data presented below for the years ended December 31, 2018 and 2019 are derived from our audited financial statements included elsewhere in this prospectus. The summary statement of operations data for the nine months ended September 30, 2019 and 2020 and balance sheet data as of September 30, 2020 are derived from our unaudited interim financial statements included elsewhere in this prospectus. The unaudited interim financial statements, in management’s opinion, have been prepared on the same basis as the audited financial statements and the related notes included elsewhere in this prospectus, and include all adjustments, consisting only of normal recurring adjustments, that management considers necessary for a fair presentation of the information for the periods presented. The following summary financial data should be read in conjunction with “Selected Financial Data,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes included elsewhere in this prospectus. Our historical results are not necessarily indicative of the results that may be expected in any future period and the results for the nine months ended September 30, 2020 are not necessarily indicative of the results that may be expected for the year ended December 31, 2020. The summary financial data in this section are not intended to replace our financial statements and are qualified in their entirety by the financial statements and related notes included elsewhere in this prospectus.

(in thousands, except share and per share data)	Year ended December 31,		Nine months ended September 30,	
	2018	2019	2019	2020
Statement of Operations Data:				
Operating expenses:				
Research and development	\$ 12,621	\$ 24,279	\$ 15,430	\$ 33,605
General and administrative	2,354	3,830	2,584	5,712
Total operating expenses	14,975	28,109	18,014	39,317
Loss from operations	(14,975)	(28,109)	(18,014)	(39,317)
Other income, net	295	539	483	1,638
Net loss	\$ (14,680)	\$ (27,570)	\$ (17,531)	\$ (37,679)
Per share information:				
Net loss per share of common stock, basic and diluted ⁽¹⁾	\$ (10.46)	\$ (16.52)	\$ (10.80)	\$ (15.83)
Weighted average common shares outstanding, basic and diluted ⁽¹⁾	1,402,928	1,668,549	1,622,546	2,380,100

(1) See Note 3 to our financial statements included elsewhere in this prospectus for a description of how we compute net loss per share of common stock, basic and diluted and the weighted average shares outstanding used in the computation of these per share amounts.

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(in thousands)	As of September 30, 2020	
	Actual	As Adjusted(1)
Balance Sheet Data:		
Cash and cash equivalents	\$ 234,792	
Working capital(2)	226,702	
Total assets	239,681	
Total stockholders' equity	228,307	

(1) As adjusted amounts reflect the sale of _____ shares of our common stock by us in this offering at the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021 after deducting the estimated underwriting discounts and commissions and estimated offering expenses. A \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, would increase (decrease) the as adjusted amount of each of cash and cash equivalents, working capital, total assets and total stockholders' equity by \$ _____ million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 1,000,000 in the number of shares offered by us in this offering would increase (decrease) the as adjusted amount of each of cash and cash equivalents, working capital, total assets and total stockholders' equity by \$ _____ million, assuming the assumed public offering price remains the same and after deducting estimated underwriting discounts commissions and estimated offering expenses payable by us.

(2) We define working capital as current assets less current liabilities. See our financial statements and related notes appearing at the end of this prospectus for further details regarding our current assets and current liabilities.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. Before making your decision to invest in shares of our common stock, you should carefully consider the risks described below, together with the other information contained in this prospectus, including our financial statements and the related notes appearing at the end of this prospectus. We cannot assure you that any of the events discussed below will not occur. These events could have a material and adverse impact on our business, financial condition, results of operations and prospects. If that were to happen, the trading price of our common stock could decline, and you could lose all or part of your investment.

Risks Related to Our Financial Position and Need for Capital

We have a limited operating history, which may make it difficult to evaluate the success of our business to date and to assess our future viability. We have incurred significant operating losses since our inception and have not generated any revenue. We expect to incur continued losses for the foreseeable future and may never achieve or maintain profitability.

Investment in drug development is a highly speculative undertaking and involves a substantial degree of risk. We commenced operations in 2016 and are a clinical-stage biopharmaceutical company with a limited operating history. We have not yet commercialized any product and we do not expect to generate revenue from sales of any products for several years, if at all. Consequently, there have been limited operations upon which we or you can evaluate our business, and predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing cancer therapies. For the year ended December 31, 2019, we reported a net loss of \$27.6 million. For the three and nine months ended September 30, 2020, we reported a net loss of \$16.8 million and \$37.7 million, respectively. As of September 30, 2020, we had an accumulated deficit of \$88.2 million. We expect to continue to incur significant research and development and other expenses related to our ongoing operations.

Since our inception, we have focused substantially all of our efforts and financial resources on the research, preclinical and clinical development of our product candidates, PRT543, PRT811 and PRT1419, and our research efforts on other potential product candidates targeting Protein Arginine Methyltransferase 5, or PRMT5, Myeloid Cell Leukemia Sequence 1, or MCL1, Cyclin-dependent kinase 9, or CDK9, and Brahma homologue, or BRM, otherwise known as SMARCA2. To date, we have funded our operations with proceeds from sales of shares of our convertible preferred stock and common stock in our initial public offering, or the IPO. From inception through September 30, 2020, we received an aggregate of \$311.0 million in net proceeds from such sales. As of September 30, 2020, our cash and cash equivalents were \$234.8 million.

We expect to incur increasing levels of operating losses for the foreseeable future, particularly as we advance PRT543, PRT811 and PRT1419 through clinical development. Our prior losses, combined with expected future losses, have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses to significantly increase in connection with our additional planned clinical trials for our lead product candidates, including the ongoing Phase 1 clinical trials and the planned expansion cohorts of PRT543 and PRT811, the ongoing Phase 1 clinical trial for PRT1419 and development and subsequent INDs of other future product candidates we may choose to pursue, including PRT2527, our CDK9 inhibitor, a SMARCA2 protein degrader and a kinase inhibitor. In addition, if we obtain marketing approval for PRT543, PRT811, PRT1419 or another product candidate, we will incur significant sales, marketing and outsourced manufacturing expenses in connection with the commercialization of PRT543, PRT811, PRT1419 or such other product candidate, respectively. We will also continue to incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our

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profitability on a quarterly or annual basis. We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval for, and begin to sell, PRT543, PRT811, PRT1419 or another product candidate. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- complete successful Phase 1 portions of PRT543, PRT811 and PRT1419 clinical trials;
- initiate and successfully complete all safety, pharmacokinetic and other studies required to obtain U.S. and foreign marketing approval for PRT543 as a treatment for patients with hematological malignancies and advanced solid tumors, PRT811 as a treatment for patients with glioblastoma and advanced solid tumors and PRT1419 as a treatment for patients with certain hematological malignancies;
- initiate and complete successful later-stage clinical trials that meet their clinical endpoints;
- obtain favorable results from our clinical trials and apply for and obtain marketing approval for PRT543, PRT811 and PRT1419;
- establish licenses, collaborations or strategic partnerships that may increase the value of our programs;
- successfully manufacture or contract with others to manufacture PRT543, PRT811, PRT1419 and our other product candidates;
- commercialize PRT543, PRT811, PRT1419, if approved, respectively, by building a sales force or entering into collaborations with third parties;
- submit INDs for PRT2527 and the SMARCA2 protein degrader that are made effective by the U.S. Food and Drug Administration, or the FDA;
- obtain, maintain, protect and defend our intellectual property portfolio; and
- achieve market acceptance of PRT543, PRT811, PRT1419 and our other successful product candidates with the medical community and with third-party payors.

To become and remain profitable, we must succeed in designing, developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials for our product candidates, designing additional product candidates, establishing arrangements with third parties for the manufacture of clinical supplies of our product candidates, obtaining marketing approval for our product candidates and manufacturing, marketing and selling any products for which we may obtain marketing approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

In cases where we are successful in obtaining regulatory approval to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement, and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved.

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Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses we will incur or when, or if, we will be able to achieve profitability. If we decide to or are required by the FDA or regulatory authorities in other jurisdictions to perform studies or clinical trials in addition to those currently expected, or if there are any delays in establishing appropriate manufacturing arrangements for, in initiating or completing our current and planned clinical trials for, or in the development of, any of our product candidates, our expenses could increase materially and profitability could be further delayed.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

Even if this offering is successful, we will require substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed or on terms acceptable to us, we could be forced to delay, reduce or eliminate our research or drug development programs, any future commercialization efforts or other operations.

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates, PRT543, PRT811 and PRT1419, and other pipeline product candidates through clinical development, and seek to design additional product candidates from our discovery programs. We expect increased expenses as we continue our research and development, initiate additional clinical trials, and seek marketing approval for our lead programs and our other product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Adequate additional financing may not be available to us on favorable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. If we are unable to raise capital when needed or on favorable terms, we could be forced to delay, reduce or eliminate our research and development programs, our commercialization plans or other operations.

We believe that the net proceeds from this offering, together with our existing cash and cash equivalents will enable us to fund our operating expenses, and capital expenditure requirements into . We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Changes beyond our control may occur that would cause us to use our available capital before that time, including changes in and progress of our drug development activities and changes in regulation. Our future capital requirements will depend on many factors, including:

- the progress, timing and results of preclinical studies and clinical trials for our current or any future product candidates;
- the extent to which we develop, in-license or acquire other pipeline product candidates or technologies;
- the number and development requirements of other product candidates that we may pursue, and other indications for our current product candidates that we may pursue;
- the costs, timing and outcome of obtaining regulatory approvals of our current or future product candidates and any companion diagnostics we may pursue;
- the scope and costs of making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our current or future product candidates;

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- the costs involved in growing our organization to the size needed to allow for the research, development and potential commercialization of our current or future product candidates;
- the cost associated with commercializing any approved product candidates, including establishing sales, marketing and distribution capabilities;
- the cost associated with completing any post-marketing studies or trials required by the FDA or other regulatory authorities;
- the revenue, if any, received from commercial sales of PRT543, PRT811, PRT1419, or PRT2527 if any are approved, or our other pipeline product candidates that receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims that we may become subject to, including any litigation costs and the outcome of such litigation;
- the costs associated with potential product liability claims, including the costs associated with obtaining insurance against such claims and with defending against such claims; and
- to the extent we pursue strategic collaborations, including collaborations to commercialize PRT543, PRT811, PRT1419, PRT2527 or any of our other pipeline product candidates, our ability to establish and maintain collaborations on favorable terms, if at all, as well as the timing and amount of any milestone or royalty payments we are required to make or are eligible to receive under such collaborations, if any.

Even if this offering is successful, we will require additional capital to complete our planned clinical development programs for our current product candidates to obtain regulatory approval. Our ability to raise additional funds will depend on financial, economic and market conditions and other factors, over which we may have no or limited control. If adequate funds are not available on commercially acceptable terms when needed, we may be forced to delay, reduce or terminate the development or commercialization of all or part of our research programs or product candidates or we may be unable to take advantage of future business opportunities. Furthermore, any additional capital-raising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our current and future product candidates, if approved.

Raising additional capital may cause dilution to our stockholders, including purchasers of common stock in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future

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commercialization efforts or grant rights to third parties to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to Design and Development of our Product Candidates

We are highly dependent on the success of our product candidates, PRT543, PRT811 and PRT1419, which are in early clinical development, and PRT2527, which is in preclinical development. We have not completed successful late-stage pivotal clinical trials or obtained regulatory approval for any product candidate. We may never obtain approval for any of our product candidates or achieve or sustain profitability.

Our future success is highly dependent on our ability to obtain regulatory approval for, and then successfully commercialize, our product candidates, PRT543, PRT811 and PRT1419. We are early in our development efforts and our lead product candidates, PRT543, PRT811 and PRT1419, are each currently in a Phase 1 clinical trial. Our other product candidates, including PRT2527, are in earlier stages of development. We currently have no products that are approved for sale in any jurisdiction. There can be no assurance that PRT543, PRT811, PRT1419, PRT2527 or our other product candidates in development will achieve success in their clinical trials or obtain regulatory approval.

Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of PRT543, PRT811, PRT1419, PRT2527 or other product candidates in development. The success of our product candidates, including PRT543, PRT811, PRT1419 and PRT2527, will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials;
- acceptance of INDs by the FDA or other similar clinical trial applications from foreign regulatory authorities for our future clinical trials for our pipeline product candidates;
- timely and successful enrollment of patients in, and completion of, clinical trials with favorable results;
- demonstration of safety, efficacy and acceptable risk-benefit profiles of our product candidates to the satisfaction of the FDA and foreign regulatory agencies;
- our ability, or that of our collaborators, to develop and obtain clearance or approval of companion diagnostics, on a timely basis, or at all;
- receipt and related terms of marketing approvals from applicable regulatory authorities, including the completion of any required post-marketing studies or trials;
- raising additional funds necessary to complete clinical development of and commercialize our product candidates;
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our product candidates;
- developing and implementing marketing and reimbursement strategies;
- establishing sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining third-party payor coverage and adequate reimbursement;

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- protecting and enforcing our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of the products following approval.

Many of these factors are beyond our control, and it is possible that none of our product candidates will ever obtain regulatory approval even if we expend substantial time and resources seeking such approval. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. For example, our business could be harmed if results of our ongoing clinical trials of PRT543, PRT811 or PRT1419, vary adversely from our expectations.

Drug development involves a lengthy and expensive process, and clinical testing is uncertain as to the outcome.

We currently have three product candidates in Phase 1 clinical development and additional product candidates in preclinical development, and the risk of failure for each is high. We are unable to predict when or if our product candidates will prove effective or safe in humans or will obtain marketing approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to the outcome.

A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials or of clinical trials of the same product candidates in other indications, and interim or preliminary results of a clinical trial do not necessarily predict final results. Later-stage clinical trials could differ in significant ways from early-stage clinical trials, including changes to inclusion and exclusion criteria, efficacy endpoints, dosing regimen and statistical design. In particular, the small number of patients in our current Phase 1 clinical trials may make the results of these trials less predictive of the outcome of later clinical trials. In addition, although we have observed encouraging clinical activity in the dose escalation portion of the Phase 1 portion of our ongoing PRT543 and PRT811 clinical trials, the primary objectives were to determine the safety, tolerability and maximum tolerated dose of PRT543 and PRT811, respectively, and to determine a recommended Phase 2 dose for the expansion portion of our Phase 1 clinical trials, and not to demonstrate efficacy. The assessments of clinical activity from this portion of the clinical trials, some of which were not pre-specified, may not be predictive of the results in dose expansion cohorts, specific tumor types or further clinical trials of PRT543 and PRT811. In addition, while we may believe certain results in patients, such as stable disease, suggest encouraging clinical activity, stable disease is not considered a response for regulatory purposes. Stable disease, or SD, is defined as failure to meet the definition of objective clinical response or progressive disease. Furthermore, safety events may be observed in later trials that alter the anticipated risk-benefit profiles of PRT543 and PRT811.

We may incur additional costs or experience delays in completing, or ultimately be unable to complete the development and/or commercialization of PRT543, PRT811, PRT1419, PRT2527 or our other product candidates.

Before we can initiate clinical trials of a product candidate in any indication, we must submit the results of preclinical studies to the FDA or to comparable foreign authorities, respectively, along with other information, including information about the product candidate's chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND or comparable foreign regulatory filings.

The FDA may require us to conduct additional preclinical studies for any product candidate before it allows us to initiate subsequent clinical trials under any IND, which may lead to additional delays and increase the costs of our preclinical development programs.

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Any delays in the commencement or completion of our ongoing, planned or future clinical trials could significantly affect our product development costs. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to obtain marketing approval or commercialize our product candidates, including:

- regulators, institutional review boards, or IRBs, or ethics committees, or ECs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- the FDA may disagree as to the design or implementation of our clinical trials or with our recommended Phase 2 doses for any of our pipeline programs;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective clinical research organizations, or CROs, and prospective trial sites;
- clinical trials for our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials, delay or halt clinical trials or abandon product development programs;
- lack of adequate funding to continue the clinical trial;
- the number of patients required for clinical trials for our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or may be lower than we anticipate due to challenges in recruiting and enrolling suitable patients that meet the study criteria, participants may drop out of these clinical trials at a higher rate than we anticipate or the duration of these clinical trials may be longer than we anticipate;
- competition for clinical trial participants from investigational and approved therapies may make it more difficult to enroll patients in our clinical trials;
- we may experience difficulties in maintaining contact with patients after treatment, resulting in incomplete data;
- we or third-party collaborators may fail to obtain regulatory approval of companion diagnostic tests, if required, on a timely basis, or at all;
- our third-party contractors may fail to meet their contractual obligations to us in a timely manner, or at all, or may fail to comply with regulatory requirements;
- we may have to suspend or terminate clinical trials for our product candidates for various reasons, including a finding by us or by a Data Monitoring Committee for a trial that the participants are being exposed to unacceptable health risks;
- our product candidates may have undesirable or unexpected side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs/ECs to suspend or terminate the trials;
- the cost of clinical trials for our product candidates may be greater than we anticipate;
- changes to clinical trial protocol;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials for our product candidates may be insufficient or inadequate and result in delays or suspension of our clinical trials; and
- the impact of the ongoing COVID-19 pandemic, which may slow potential enrollment, reduce the number of eligible patients for clinical trials, or reduce the number of patients that remain in our trials.

Delays, including delays caused by the above factors, can be costly and could negatively affect our ability to complete a clinical trial or obtain timely marketing approvals. We do not know whether any of our planned

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preclinical studies or clinical trials will begin on a timely basis or at all, will need to be restructured or will be completed on schedule, or at all. For example, the FDA may place a partial or full clinical hold on any of our clinical trials for a variety of reasons, including safety concerns and noncompliance with regulatory requirements. If we are not able to complete successful clinical trials, we will not be able to obtain regulatory approval and will not be able to commercialize our product candidates.

Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If we experience delays or difficulties in enrolling patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approval could be delayed or prevented.

We may not be able to initiate or continue our ongoing or planned clinical trials for our product candidates if we are unable to identify and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or comparable foreign regulatory authorities. In addition, some of our competitors currently have ongoing clinical trials for product candidates that would treat the same patients as our clinical product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. This is acutely relevant for our development of PRT543 for the treatment of patients with myeloid malignancies and other solid tumors, including adenoid cystic carcinoma, or ACC, indications for which investigational drugs by our competitors are competing for clinical trial participants. Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- our ability to recruit clinical trial investigators of appropriate competencies and experience;
- the incidence and prevalence of our target indications;
- clinicians' and patients' awareness of, and perceptions as to the potential advantages and risks of our product candidates in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- competing studies or trials with similar eligibility criteria;
- invasive procedures required to enroll patients and to obtain evidence of the product candidate's performance during the clinical trial;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria defined in the protocol for the trial in question;
- the size and nature of the patient population required for analysis of the trial's primary endpoints;
- efforts to facilitate timely enrollment in clinical trials;
- whether we are subject to a partial or full clinical hold on any of our clinical trials;
- reluctance of physicians to encourage patient participation in clinical trials;
- the ability to monitor patients adequately during and after treatment;
- our ability to obtain and maintain patient consents; and
- proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll and maintain a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials, including due to the COVID-19 pandemic, may result in increased development costs, which would cause the value of our company to decline and limit our ability to obtain additional financing.

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The COVID-19 pandemic could adversely impact our business, including our clinical trials and clinical trial operations.

The COVID-19 pandemic in the United States and in other countries in which we have planned or have active clinical trial sites and where our third-party manufacturers operate, could cause significant disruptions that could severely impact our business and clinical trials, including:

- delays or difficulties in screening, enrolling and maintaining patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- inability or unwillingness of subjects to travel to the clinical trial sites;
- delays, difficulties, or incompleteness in data collection and analysis and other related activities;
- decreased implementation of protocol required clinical trial activities and quality of source data verification at clinical trial sites;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others;
- limitations in employee resources that would otherwise be focused on the conduct of our clinical trials and our other research and development activities, including because of sickness of employees or their families or mitigation measures such as lock-downs and social distancing;
- delays due to production shortages resulting from any events affecting raw material supply or manufacturing capabilities domestically and abroad;
- delays in receiving approval from local regulatory authorities to initiate our planned clinical trials;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials;
- interruption in global and domestic shipping that may affect the transport of clinical trial materials, such as investigational drug products used in our clinical trials;
- changes in local regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, delays, or to discontinue the clinical trials altogether;
- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees;
- refusal of regulatory authorities such as FDA or European Medicines Agency, or EMA, to accept data from clinical trials in affected geographies; and
- adverse impacts on global economic conditions which could have an adverse effect on our business and financial condition, including impairing our ability to raise capital when needed.

Such disruptions could impede, delay, limit or prevent completion of our ongoing clinical trials and preclinical studies or commencement of new clinical trials and ultimately lead to the delay or denial of regulatory approval of our product candidates, which would seriously harm our operations and financial condition and increase our costs and expenses. We are in close contact with our CROs, CMOs and clinical sites as we seek to mitigate the impact of COVID-19 on our studies and current timelines. Measures we have taken in response to COVID-19 include, where feasible, conducting remote clinical trial site activations and data monitoring, and limiting on-site patient visits by adjusting patient assessments and protocol. However, despite these efforts, we have experienced limited delays in trial site initiations, patient participation and patient enrollment in some of our

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clinical trials and we may continue to experience some delays in our clinical trials and preclinical studies and delays in data collection and analysis. These delays so far have had a limited impact, but this may change as the COVID-19 pandemic and the response to such COVID-19 pandemic continues to evolve, and could have an adverse impact on our timelines and our business. The COVID-19 pandemic could also affect the business of the FDA, EMA or other health authorities, which could result in delays in meetings related to planned or completed clinical trials and ultimately of reviews and approvals of our product candidates. The global COVID-19 pandemic continues to rapidly evolve. The extent to which the COVID-19 pandemic may impact our business and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease.

Adverse side effects or other safety risks associated with PRT543, PRT811, PRT1419 or our other product candidates could delay or preclude approval, cause us to suspend or discontinue clinical trials or abandon further development, limit the commercial profile of an approved product, or result in significant negative consequences following marketing approval, if any.

As is the case with pharmaceuticals generally, we have observed side effects and adverse events associated with our clinical product candidate, PRT543. These side effects included diarrhea, nausea and fatigue, but none of these side effects were considered related to PRT543. At the highest dose level of our clinical product candidate, PRT543, there were occurrences of grade 4 thrombocytopenia that were deemed related to PRT543, but the toxicity was reversible after a one to two week drug holiday and the affected patients remained on the study and were restarted at a lower dose. We have also observed side effects and adverse effects associated with PRT811. These side effects included nausea, constipation, vomiting and hyponatremia, but none of these side effects were considered related to PRT811.

Results of our ongoing and planned clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could result in the delay, suspension or termination of clinical trials by us or regulatory authorities for a number of reasons. Furthermore, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of subjects and limited duration of exposure, rare and severe side effects of our product candidates or those of our competitors may only be uncovered with a significantly larger number of patients exposed to the drug.

Additionally, due to the high mortality rates of the cancers for which we are initially pursuing development and the pretreated nature of many patients in our ongoing clinical trials of PRT543, PRT811 and PRT1419, a material percentage of patients in these clinical trials may die during a trial, which could impact development of PRT543, PRT811 and PRT1419, respectively. If we elect or are required to delay, suspend or terminate any clinical trial, the commercial prospects of our product candidates will be harmed and our ability to generate product revenues from this product candidate will be delayed or eliminated. Serious adverse events, or SAEs, observed in clinical trials could hinder or prevent market acceptance of our product candidates. Any of these occurrences may harm our business, prospects, financial condition and results of operations significantly.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for our product candidates, if approved. We may also be required to modify our study plans based on findings in our clinical trials. Such side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial. Many drugs that initially showed promise in early stage testing have later been found to cause side effects that prevented further development. In addition, regulatory authorities may draw different conclusions, require

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additional testing to confirm these determinations, require more restrictive labeling, or deny regulatory approval of the product candidate.

It is possible that, as we test our product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens, or as the use of our product candidates becomes more widespread following any regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition, results of operations and prospects significantly.

In addition, if any of our product candidates receive marketing approval, and we or others later identify undesirable side effects caused by treatment with such drug, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approval of the drug;
- we may be required to recall a product or change the way the drug is administered to patients;
- regulatory authorities may require additional warnings in the labeling, such as a contraindication or a boxed warning, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- additional restrictions may be imposed on the marketing or promotion of the particular product or the manufacturing processes for the product or any component thereof;
- we could be sued and held liable for harm caused to patients;
- we may be subject to regulatory investigations and government enforcement actions;
- the drug could become less competitive; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates, if approved, and could significantly harm our business, financial condition, results of operations and prospects.

Preliminary, interim and topline data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary, interim or topline data from our clinical trials, such as the preliminary data analysis for the Phase 1 dose expansion portions of our PRT543 and PRT811 trials. These updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. Additionally, interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Therefore, positive interim results in any ongoing clinical trial may not be predictive of such results in the completed study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final

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data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. In addition, we may report interim analyses of only certain endpoints rather than all endpoints. Adverse changes between preliminary or interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock after this offering. See the description of risks under the heading “Risks Related to our Common Stock and This Offering” for more disclosure related to the risk of volatility in our stock price.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. You or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the preliminary or topline data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, PRT543, PRT811 or PRT1419, or any other product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We may not be successful in our efforts to design additional potential product candidates.

A key element of our strategy is to identify molecular targets and intervention points leading to treatment failure, and then apply our expertise of cancer biology and medicinal chemistry, as well as our in-depth understanding of the current landscape of oncology treatments, to design solutions that can be precisely tailored in a target class agnostic fashion. The therapeutic design and development activities that we are conducting may not be successful in developing product candidates that are safe and effective in treating cancer or other diseases. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the target selection methodology used may not be successful in identifying potential product candidates;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will obtain marketing approval or achieve market acceptance; or
- potential product candidates may not be effective in treating their targeted diseases.

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Research programs to identify and design new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. If we are unable to identify and design suitable product candidates for preclinical and clinical development, we will not be able to obtain revenues from the sale of products in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

Risks Related to Government Regulation

The development and commercialization of pharmaceutical products are subject to extensive regulation, and we may not obtain regulatory approvals for PRT543, PRT811, PRT1419, PRT2527 or any other product candidates, on a timely basis or at all.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, import, marketing, distribution, adverse event reporting, including the submission of safety and other post-marketing information and reports, and other possible activities relating to PRT543, PRT811 and PRT1419, currently our only product candidates in planned or ongoing clinical trials, as well as any other product candidate that we may develop in the future, are subject to extensive regulation. Marketing approval of drugs in the United States requires the submission of an NDA to the FDA, and we are not permitted to market any product candidate in the United States until we obtain approval from the FDA of the NDA for that product. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. Our product candidates must be approved by comparable regulatory authorities in other jurisdictions prior to commercialization.

FDA approval of an NDA is not guaranteed, and the review and approval process is an expensive and uncertain process that may take several years. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, there can be no assurance that any of our product candidates will receive regulatory approval in the United States, or other jurisdictions.

The FDA also has substantial discretion in the approval process. The number and types of preclinical studies and clinical trials that will be required for NDA approval varies depending on the product candidate, the disease or the condition that the product candidate is designed to treat and the regulations applicable to any particular product candidate. For example, if successful, we believe that the expansion portions of the Phase 1 clinical trials of PRT543 or PRT811 may be sufficient to support FDA approval of an NDA for PRT543 or PRT811, respectively, but the FDA may disagree with the sufficiency of our data and require additional clinical trials. Additionally, depending upon the results of the expansion portions of the Phase 1 clinical trials of PRT543 or PRT811, we may choose to seek Subpart H accelerated approval for PRT543 or PRT811, respectively, which would require completion of a confirmatory trial to validate the clinical benefit of the drug. Despite the time and expense associated with preclinical studies and clinical trials, failure can occur at any stage. The results of preclinical and early clinical trials of PRT543, PRT811, PRT1419, PRT2527 or any other product candidate may not be predictive of the results of our later-stage clinical trials.

Clinical trial failure may result from a multitude of factors including flaws in trial design, dose selection, placebo effect, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits, and failure in clinical trials can occur at any stage. Companies in the pharmaceutical industry frequently suffer setbacks in the advancement of clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Based upon negative or inconclusive results, we may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. In addition, data obtained from clinical trials are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may further delay, limit or prevent marketing approval.

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The FDA could delay, limit or deny approval of a product candidate for many reasons, including because the FDA:

- may not deem our product candidate to be safe and effective;
- determines that the product candidate does not have an acceptable benefit-risk profile;
- determines in the case of an NDA seeking accelerated approval that the NDA does not provide evidence that the product candidate represents a meaningful advantage over available therapies;
- determines that the objective response rate, or ORR, and duration of response are not clinically meaningful;
- may not agree that the data collected from preclinical studies and clinical trials are acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval, and may impose requirements for additional preclinical studies or clinical trials;
- may determine that adverse events experienced by participants in our clinical trials represent an unacceptable level of risk;
- may determine that population studied in the clinical trial may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- may not accept clinical data from trials, which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States;
- may disagree regarding the formulation, labeling and/or the specifications;
- may not approve the manufacturing processes associated with our product candidate or may determine that a manufacturing facility does not have an acceptable compliance status;
- may change approval policies or adopt new regulations; or
- may not file a submission due to, among other reasons, the content or formatting of the submission.

We have not obtained FDA approval for any product. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for our clinical product candidates.

If we experience delays in obtaining approval or if we fail to obtain approval of PRT543, PRT811 or PRT1419, our commercial prospects will be harmed and our ability to generate revenues will be materially impaired which would adversely affect our business, prospects, financial condition and results of operations.

The accelerated approval pathway for our product candidates may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

Under the FDA's accelerated approval program, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. We may seek accelerated approval for one or more of our product candidates on the basis of ORR with an acceptable duration of response, a surrogate endpoint that we believe is reasonably likely to predict clinical benefit.

For drugs granted accelerated approval, post-marketing confirmatory trials are required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence and, in some cases, the FDA may require that the trial be designed, initiated,

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and/or fully enrolled prior to approval. If any of our competitors were to receive full approval on the basis of a confirmatory trial for an indication for which we are seeking accelerated approval before we receive accelerated approval, the indication we are seeking may no longer qualify as a condition for which there is an unmet medical need and accelerated approval of our product candidate would be more difficult or may not occur. Moreover, the FDA may withdraw approval of our product candidate approved under the accelerated approval pathway if, for example:

- the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug;
- other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use;
- we fail to conduct any required post-approval trial of our product candidate with due diligence; or
- we disseminate false or misleading promotional materials relating to the relevant product candidate.

Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in those jurisdictions, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our products in any jurisdiction outside the United States, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to submit for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

We may not be able to obtain or maintain orphan drug designation or exclusivity for our product candidates.

Regulatory authorities in some jurisdictions, including the United States, may designate drugs for relatively small patient populations as “orphan drugs.” Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States, or if the disease or condition affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing the drug for the type of disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. Additionally, if a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years, except in certain circumstances, such as a showing of clinical superiority (i.e., another product is safer, more effective or makes a major contribution to patient care) over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity, or obtain approval for the same product but for a different indication than that for which the orphan product has exclusivity.

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We may apply for an orphan drug designation in the United States or other geographies for our product candidates in the future. However, obtaining an orphan drug designation can be difficult, and we may not be successful in doing so. Even if we obtain orphan drug designation for our product candidates in specific indications, we may not be the first to obtain regulatory approval of these product candidates for the orphan-designated indication, due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for orphan designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Orphan drug designation does not ensure that we will receive marketing exclusivity in a particular market, and we cannot assure you that any future application for orphan drug designation in any other geography or with respect to any other product candidate will be granted. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process.

A Breakthrough Therapy Designation by the FDA for any of our current or future product candidates may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that the product candidate will receive marketing approval.

We may seek a Breakthrough Therapy Designation for one or more of our current or future product candidates. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for priority review if supported by clinical data at the time of the submission of the NDA.

Designation as a breakthrough therapy is at the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a drug may not result in a faster development process, review, or approval compared to drugs considered for approval under conventional FDA procedures and it would not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidate no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened.

If we are unable to successfully develop, validate, obtain regulatory approval of and commercialize companion diagnostic tests for any product candidates that require such tests, or experience significant delays in doing so, we may not realize the full commercial potential of these product candidates.

A companion diagnostic is a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding therapeutic drug product. A companion diagnostic can be used to identify patients who are most likely to benefit from the therapeutic product. In the future, we may evaluate opportunities to develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications.

A companion diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product. To date, the FDA has required premarket approval of all companion diagnostics for cancer therapies. Generally, when a companion diagnostic is essential to the safe and effective use of a drug product, the FDA requires that the companion diagnostic be approved before or concurrent with approval of the therapeutic product and before a product can be commercialized. The approval of a companion diagnostic as part of the

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therapeutic product's labeling limits the use of the therapeutic product to only those patients who express the specific genetic alteration that the companion diagnostic was developed to detect.

Development of a companion diagnostic could include additional meetings with regulatory authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption application. In the case of a companion diagnostic that is designated as "significant risk device," approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate.

To be successful in developing, validating, obtaining approval of and commercializing a companion diagnostic, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for companion diagnostic tests on our own, we will require additional personnel. We may rely on third parties for the design, development, testing, validation and manufacture of companion diagnostic tests for our therapeutic product candidates that require such tests, the application for and receipt of any required regulatory approvals, and the commercial supply of these companion diagnostics. If these parties are unable to successfully develop companion diagnostics for these therapeutic product candidates, or experience delays in doing so, we may be unable to enroll enough patients for our current and planned clinical trials, the development of these therapeutic product candidates may be adversely affected, these therapeutic product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of these therapeutics that obtain marketing approval. For any product candidate for which a companion diagnostic is necessary to select patients who may benefit from use of the product candidate, any failure to successfully develop a companion diagnostic may cause or contribute to delayed enrollment of our clinical trials, and may prevent us from initiating a pivotal trial. In addition, the commercial success of any of our product candidates that require a companion diagnostic will be tied to and dependent upon the receipt of required regulatory approvals and the continued ability of such third parties to make the companion diagnostic commercially available to us on reasonable terms in the relevant geographies. Any failure to do so could materially harm our business, results of operations and financial condition.

If we decide to pursue a Fast Track Designation by the FDA, it may not lead to a faster development or regulatory review or approval process.

We may seek Fast Track Designation for one or more of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the product sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

Even if we obtain marketing approval for our product candidates, the terms of approvals, ongoing regulation of our products or other post-approval restrictions may limit how we manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Any product candidates for which we receive accelerated approval from the FDA are required to undergo one or more confirmatory clinical trials. If such a product candidate fails to meet its safety and efficacy endpoints in such confirmatory clinical trials, the regulatory authority may withdraw its conditional approval. There is no assurance that any such product will successfully advance through its confirmatory clinical trial(s). Therefore, even if a product candidate receives accelerated approval from the FDA, such approval may be withdrawn at a later date.

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Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, which may include the requirement to implement a REMS or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product.

We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to ensure that quality control and manufacturing procedures conform to current good manufacturing practices, or cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our contract manufacturing organizations, or CMOs, could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we obtain marketing approval for one or more of our product candidates, we and our CMOs will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. As a result, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we obtain marketing approval will be subject to ongoing enforcement of post-marketing requirements by regulatory agencies, and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding drug distribution and the distribution of samples to physicians and recordkeeping.

The FDA and other federal and state agencies, including the Department of Justice, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. For example, the FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. Violations of such requirements may lead to investigations alleging violations of the Federal Food, Drug, and Cosmetic Act, or FDCA, and other statutes, including the False Claims Act and other federal and state healthcare fraud and abuse laws as well as state consumer protection laws. Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;

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- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Non-compliance by us or any future collaborator with regulatory requirements, including safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population can also result in significant financial penalties.

Our current and future relationships with customers and third-party payors may be subject to applicable anti-kickback, fraud and abuse, transparency, health privacy, and other healthcare laws and regulations, which could expose us to significant penalties, including criminal, civil, and administrative penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, including physicians, and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research, as well as, market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations that may be applicable to our business include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal civil, including the False Claims Act, which can be enforced by civil whistleblower or qui tam actions on behalf of the government, and criminal false claims laws and the civil monetary penalties law, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any

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healthcare benefit program, regardless of the payor (e.g. public or private), and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates and their subcontractors that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security, and transmission of such individually identifiable health information;
- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA, requires certain manufacturers of drugs, devices, biologics and medical supplies to annually report to the Centers for Medicare & Medicaid Services, or CMS, information related to payments and other transfers of value provided to, and ownership and investment interests held by, physicians, defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified nurse anesthetists and certified nurse-midwives; and
- analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance regulations promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures, or drug pricing, including price increases. State and local laws require the registration of pharmaceutical sales representatives. State and non-U.S. laws that also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil and administrative sanctions, including exclusions from government funded healthcare programs, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

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Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and decrease the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

For example, in March 2010, the former U.S. President signed into law the ACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the ACA of importance to our potential product candidates are the following:

- annual fees and taxes on manufacturers of certain branded prescription drugs;
- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report financial arrangements with physicians, as defined by such law, and teaching hospitals;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There remain judicial and Congressional challenges as well as efforts by the current U.S. President's administration to repeal or replace certain aspects of the ACA. Since January 2017, the current U.S. President has signed Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing penalties, starting January 1, 2019, for not complying with the ACA's

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individual mandate to carry health insurance, eliminating the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the United States Supreme Court is currently reviewing this case, although it is unclear when a decision will be made. It is unclear how such litigation and other efforts to repeal and replace the ACA will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals for spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction, triggering the legislation's automatic reduction to several government programs. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which began in 2013, and due to subsequent legislative amendments to the statute, will remain in effect through 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding.

Further, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the current U.S. President's administration issued budget proposals for fiscal year 2021 includes a \$135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. In addition, the Trump administration previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contained proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers.

On July 24, 2020 and September 13, 2020, the current U.S. President announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. As a result, the FDA also released a final rule on September 24, 2020 providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. The U.S. Department of Health and Human Services, or HHS, also published an interim final rule that establishes a Most Favored Nation, or MFN, Model for Medicare Part B drug payment. This regulation would substantially change the drug

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reimbursement landscape as it bases Medicare Part B payment for 50 selected drugs on prices in foreign countries instead of average sales price, or ASP, and establishes a fixed add-on payment in place of the current 6 percent (4.3 percent after sequestration) of ASP. The MFN drug payment amount is expected to be lower than the current ASP-based payment limit because U.S. drug prices are generally the highest in the world. Although the MFN Model payment methodology is scheduled to begin on January 1, 2021, it faces uncertain prospects for implementation. Among other things, a change in administration or litigation challenging the regulation could delay or halt its implementation.

The U.S. Department of Health and Human Services, or HHS, recently published an interim final rule that establishes a Most Favored Nation, or MFN, Model for Medicare Part B drug payment. This regulation would substantially change the drug reimbursement landscape as it bases Medicare Part B payment for 50 selected drugs on prices in foreign countries instead of average sales price, or ASP, and establishes a fixed add-on payment in place of the current 6 percent (4.3 percent after sequestration) of ASP. The MFN drug payment amount is expected to be lower than the current ASP-based payment limit because U.S. drug prices are generally the highest in the world. Although the MFN Model interim final rule with comment period is effective as of November 27 and the model payment methodology is scheduled to begin on January 1, 2021, it faces uncertain prospects for implementation. Among other things, a change in administration or litigation challenging the regulation could delay or halt its implementation.

At the state level, individual states have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. It is also possible that additional governmental action is taken to address the COVID-19 pandemic.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the countries of the European Union, or the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel trade, such as arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries. In addition, the recent withdrawal of the United Kingdom from its

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membership in the EU, often referred to as “Brexit”, could lead to legal and regulatory uncertainty in the United Kingdom and may lead to the United Kingdom and EU adopting divergent laws and regulations, including those related to the pricing of prescription pharmaceuticals, as the United Kingdom determines which EU laws to replicate or replace. If the United Kingdom were to significantly alter its regulations affecting the pricing of prescription pharmaceuticals, we could face significant new costs. As a result, Brexit could impair our ability to transact business in the EU and the United Kingdom.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates and products outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or the SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA’s accounting provisions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We and our third-party contractors are subject to numerous foreign, federal, state and local environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources, including any available insurance.

In addition, our leasing and operation of real property may subject us to liability pursuant to certain of these laws or regulations. Under existing U.S. environmental laws and regulations, current or previous owners or

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operators of real property and entities that disposed or arranged for the disposal of hazardous substances may be held strictly, jointly and severally liable for the cost of investigating or remediating contamination caused by hazardous substance releases, even if they did not know of and were not responsible for the releases.

We could incur significant costs and liabilities which may adversely affect our financial condition and operating results for failure to comply with such laws and regulations, including, among other things, civil or criminal fines and penalties, property damage and personal injury claims, costs associated with upgrades to our facilities or changes to our operating procedures, or injunctions limiting or altering our operations.

Although we maintain liability insurance to cover us for costs and expenses we may incur due to injuries to our employees, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations, which are becoming increasingly more stringent, may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We are subject to certain U.S. and certain foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations. We can face serious consequences for violations.

U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations prohibit, among other things, companies and their employees, agents, CROs, CMOs, legal counsel, accountants, consultants, contractors and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of these laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We also expect our non-U.S. activities to increase over time. We expect to rely on third parties for research, preclinical studies and clinical trials and/or to obtain necessary permits, licenses, patent registrations and other marketing approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

Risks Related to Our Reliance on Third Parties

We rely, and intend to continue to rely, on third parties to conduct our clinical trials and perform some of our research and preclinical studies. If these third parties do not satisfactorily carry out their contractual duties, fail to comply with applicable regulatory requirements or do not meet expected deadlines, our development programs may be delayed or subject to increased costs or we may be unable to obtain regulatory approval, each of which may have an adverse effect on our business, financial condition, results of operations and prospects.

We do not have the ability to independently conduct all aspects of our preclinical testing or clinical trials ourselves. As a result, we are dependent on third parties to conduct our ongoing and planned clinical trials of PRT543, PRT811 and PRT1419, and any preclinical studies and clinical trials of any other product candidates. The timing of the initiation and completion of these trials will therefore be partially controlled by such third

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parties and may result in delays to our development programs. Specifically, we expect CROs, clinical investigators and consultants to play a significant role in the conduct of these trials and the subsequent collection and analysis of data. However, these CROs and other third parties are not our employees, and we will not be able to control all aspects of their activities. Nevertheless, we are responsible for ensuring that each clinical trial is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with good clinical practices, or GCP, requirements, which are regulations and guidelines enforced by the FDA for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical trial investigators and clinical trial sites. If we or any of our CROs or clinical trial sites fail to comply with applicable GCP requirements, the data generated in our clinical trials may be deemed unreliable, and the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure or the failure of third parties on whom we rely to comply with these regulations may require us to stop and/or repeat clinical trials, which would delay the marketing approval process.

There is no guarantee that any such CROs, clinical trial investigators or other third parties on which we rely will devote adequate time and resources to our development activities or perform as contractually required. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, otherwise perform in a substandard manner, or terminate their engagements with us, the timelines for our development programs may be extended or delayed or our development activities may be suspended or terminated. If our clinical trial site terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in such clinical trial unless we are able to transfer those subjects to another qualified clinical trial site, which may be difficult or impossible.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors for whom they may also be conducting clinical trials or other pharmaceutical product development activities that could harm our competitive position. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for PRT543, PRT811, PRT1419 or any other product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products.

Manufacturing pharmaceutical products is complex and subject to product loss for a variety of reasons. We rely on third-party suppliers, including single source suppliers, to manufacture preclinical and clinical supplies of our product candidates and we intend to rely on third parties to produce commercial supplies of any approved product candidate. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, product development purposes, to support regulatory application submissions, as well as for commercial manufacture if any of our product candidates obtain marketing approval. In addition, we expect to contract with analytical laboratories for release and stability testing of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. In addition, the ongoing COVID-19 pandemic may result in disruptions to the operations or an extended shutdown of certain businesses, which could include certain of our contract manufacturers.

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We may be unable to establish any agreements with third-party manufacturers or do so on favorable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory, compliance and quality assurance;
- reliance on the third party for product development, analytical testing, and data generation to support regulatory applications;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier, the issuance of an FDA Form 483 notice or warning letter, or other enforcement action by FDA or other regulatory authority;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- carrier disruptions or increased costs that are beyond our control; and
- failure to deliver our drugs under specified storage conditions and in a timely manner.

We have only limited supply arrangements in place with respect to our product candidates, and these arrangements do not extend to commercial supply. We acquire many key materials on a purchase order basis. As a result, we do not have long-term committed arrangements with respect to our product candidates and other materials. We will need to establish one or more agreements with third parties to develop and scale up the drug manufacturing process, conduct drug testing, and generate data to support a regulatory submission. If we obtain marketing approval for any of our product candidates, we will need to establish an agreement for commercial manufacture with a third party.

In addition, we are dependent on a sole supplier for certain components of our manufacturing process. Even if we are able to replace any raw materials or other materials with an alternative, such alternatives may cost more, result in lower yields or not be as suitable for our purposes. In addition, some of the materials that we use to manufacture our product candidates are complex materials, which may be more difficult to substitute. Therefore, any disruptions arising from our sole suppliers could result in delays and additional regulatory submissions.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. If the FDA determines that our CMOs are not in compliance with FDA laws and regulations, including those governing cGMPs, the FDA may deny a new drug application, or NDA, approval until the deficiencies are corrected or we replace the manufacturer in our application with a manufacturer that is in compliance. Moreover, our failure, or the failure of our third-party manufacturers and suppliers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products. In addition, approved products and the facilities at which they are manufactured are required to maintain ongoing compliance with extensive FDA requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to cGMP requirements. As such, our CMOs are subject to continual review and periodic inspections to assess compliance with cGMPs. Furthermore, although we do not have day-to-day control over the operations of our CMOs, we are responsible for ensuring compliance with applicable laws and regulations, including cGMPs.

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In addition, our third-party manufacturers and suppliers are subject to numerous environmental, health and safety laws and regulations, including those governing the handling, use, storage, treatment and disposal of waste products, and failure to comply with such laws and regulations could result in significant costs associated with civil or criminal fines and penalties for such third parties. Based on the severity of regulatory actions that may be brought against these third parties in the future, our clinical or commercial supply of drug and packaging and other services could be interrupted or limited, which could harm our business.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. As a result, we may not obtain access to these facilities on a priority basis or at all. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

As we prepare for later-stage clinical trials and potential commercialization, we will need to take steps to increase the scale of production of our product candidates. We have not yet scaled up the manufacturing process for any of our product candidates. Third party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up or commercial activities. For example, if microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current CMOs for preclinical and clinical testing cannot perform as agreed, we may be required to replace such CMOs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement manufacturer or be able to reach agreement with any alternative manufacturer. Further, our third-party manufacturers may experience manufacturing or shipping difficulties due to resource constraints or as a result of natural disasters, labor disputes, unstable political environments, or public health epidemics such as the recent COVID-19 pandemic. If our current third-party manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that obtain marketing approval on a timely and competitive basis.

We may enter into collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We may seek third-party collaborators for the development and commercialization of some of our product candidates on a select basis. We have not entered into any collaborations to date. Our likely collaborators for any future collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a future collaboration will depend, among other things, upon our assessment of the future collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors.

If we do enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our future

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collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements. Collaborations with future collaborators involving our product candidates would pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may de-emphasize or not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus, including as a result of a sale or disposition of a business unit or development function, or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- a collaborator with marketing and distribution rights to multiple products may not commit sufficient resources to the marketing and distribution of our product relative to other products;
- collaborators may not properly obtain, maintain, defend or enforce our intellectual property rights or may use our proprietary information and intellectual property in such a way as to invite litigation or other intellectual property related proceedings that could jeopardize or invalidate our proprietary information and intellectual property or expose us to potential litigation or other intellectual property related proceedings;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all; and
- if a future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we establish one or more collaborations, all of the risks relating to product development, regulatory approval and commercialization described herein would also apply to the activities of any such future collaborators.

Risks Related to Commercialization of our Product Candidates

The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue potential and ability to achieve profitability will be adversely affected.

The total addressable market opportunity for PRT543, PRT811, PRT1419 and any other product candidates we may develop will ultimately depend upon, among other things, the diagnosis criteria included in the final

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labeling for each such product candidate if our product candidates are approved for sale for these indications, acceptance by the medical community, patient access, drug and any related companion diagnostic pricing and their reimbursement. We may initially seek regulatory approval of some of our product candidates as therapies for relapsed or refractory patients. The number of patients in our targeted commercial markets and elsewhere may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our drugs, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business.

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, current cancer treatments, such as existing targeted therapies, chemotherapy, and radiation therapy, are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the acceptance of our product candidates as front-line treatment for various indications;
- the prevalence and severity of any side effects, in particular compared to alternative treatments;
- limitations or warnings contained in the labeling approved for our product candidates by the FDA;
- the size of the target patient population;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the strength of marketing and distribution support;
- publicity for our product candidates and competing products and treatments;
- the existence of distribution and/or use restrictions, such as through a REMS;
- the availability of third-party payor coverage and adequate reimbursement;
- the timing of any marketing approval in relation to other product approvals;
- support from patient advocacy groups; and
- any restrictions on the use of our products together with other medications.

We currently have no marketing and sales organization and have no experience as a company in commercializing products and we may have to invest significant resources to develop these capabilities. If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our products, we may not be able to generate revenue.

We currently have no sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish sales, marketing and distribution capabilities, either ourselves or through collaboration or other arrangements with third parties.

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There are risks involved with establishing our own sales and marketing capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts are expected to be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- our inability to raise financing necessary to build our commercialization infrastructure;
- the inability of sales personnel to obtain access to physicians or educate an adequate number of physicians as to the benefits of our products;
- unfavorable third-party payor coverage and reimbursement in any geography;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales and marketing services, our product revenues and our profitability, if any, are likely to be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to market and sell our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of these third parties may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates for which we receive marketing approval.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of pharmaceutical products is highly competitive. We face competition with respect to our current product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and existing or emerging biotechnology companies, academic research institutions and governmental agencies and public and private research institutions worldwide. There are a number of pharmaceutical and biotechnology companies that currently are pursuing the development of precision oncology therapies optimized to effectively target the key driver mechanisms in cancers with high unmet need, including Black Diamond Therapeutics, Inc., Constellation Pharmaceuticals, Inc., Kronos Bio, Inc., Repare Therapeutics Inc., Revolution Medicines, Inc., Relay Therapeutics, Inc., and Zentalis Pharmaceuticals, LLC. In addition, we may face competition from companies pursuing the development of product candidates that are based on targeting pathways of adaptive resistance, including Amgen Inc., or Amgen, AbbVie Inc., or AbbVie, AstraZeneca PLC, or AstraZeneca, GlaxoSmithKline plc, or GlaxoSmithKline, Johnson & Johnson, Pfizer Inc., or Pfizer, Bayer AG, or Bayer, and Novartis International AG, or Novartis.

Specifically, with respect to our lead product candidates, we expect that our current product candidates PRT543 and PRT811 will compete against other PRMT5 inhibitors which are currently in clinical development, including those of GlaxoSmithKline (GSK3326595), Johnson & Johnson (JNJ-64619178) and Pfizer (PF-06939999). Development efforts and clinical results of these other product candidates may be unsuccessful, which could result in a negative perception of PRMT5 inhibitors, for instance, and negatively impact the

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regulatory approval process of our product candidates, which would have a material and adverse effect on our business. For our product candidate PRT1419, other companies are developing MCL1 inhibitors with monotherapy and/or combination trials ongoing, including Amgen (AMG176), AstraZeneca (AZD5991) and Novartis (MIK665). For our preclinical CDK9 program, AstraZeneca, Bayer and Kronos Bio have CDK9 programs in Phase 1 clinical trials.

Many of the companies against which we are competing or against which we may compete in the future, either alone or through collaborations, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and sales and marketing personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Furthermore, we also face competition more broadly across the oncology market for cost-effective and reimbursable cancer treatments. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates, if any are approved, may compete with these existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates may not be competitive with them. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. As a result, obtaining market acceptance of, and gaining significant share of the market for, any of our product candidates that we successfully introduce to the market may pose challenges. In addition, many companies are developing new oncology therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient to administer, are less expensive or with a more favorable labeling than our current or future product candidates. Our competitors also may obtain FDA, foreign regulatory authority, or other marketing or regulatory approval for their products more rapidly than any approval we may obtain for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product candidate in a particular country, but then be

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subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues, if any, we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if such product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors, including government healthcare programs, private health insurers and other organizations. Third-party payors decide which medications they will pay for and establish reimbursement levels. In the United States, the principal decisions about reimbursement for new medicines are typically made by the CMS, which decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors often, but not always, follow CMS's decisions regarding coverage and reimbursement.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining coverage and adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

Additionally, we may develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. We, or our collaborators, if any, will be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved. While we have not yet developed any companion diagnostic test for our product candidates, if we do, there is significant uncertainty regarding our ability to obtain coverage and adequate reimbursement for the same reasons applicable to our product candidates.

There may also be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, intellectual property, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies, but also have their own methods and approval process apart from Medicare determinations. Our inability to promptly obtain coverage and adequate reimbursement rates from third-party payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

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Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercialize any products that we may develop. If we cannot successfully defend ourselves against any claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- initiation of investigations by regulators;
- withdrawal of clinical trial participants;
- significant time and costs to defend the related litigation;
- diversion of management and scientific resources from our business operations;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Our current product liability insurance coverage for the United States and certain other jurisdictions may not be adequate to cover all liabilities that we may incur. We likely will need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. A successful product liability claim or series of claims brought against us could decrease our cash and adversely affect our business and financial condition.

Risks Related to Employee Matters and Our Operations

Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel and manage our human capital.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the development and management expertise of Kris Vaddi, Ph.D., our founder and Chief Executive Officer, as well as the other principal members of our management, scientific and clinical team. We currently do not maintain key person insurance on these individuals. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time.

Our industry has experienced a high rate of turnover in recent years. Our ability to compete in the highly competitive pharmaceuticals industry depends upon our ability to attract, retain and motivate highly skilled and experienced personnel with scientific, clinical, regulatory, manufacturing and management skills and experience. We conduct our operations in the greater Delaware area, a region that is home to other pharmaceutical companies as well as many academic and research institutions, resulting in fierce competition for qualified personnel. We may not be able to attract or retain qualified personnel in the future due to the intense competition for a limited number of qualified personnel among pharmaceutical companies. Many of the other pharmaceutical companies against which we compete have greater financial and other resources, different risk profiles and a longer history in the industry than we do. Our competitors may provide higher compensation, more diverse opportunities and/or better opportunities for career advancement. Any or all of these competing factors may limit our ability to

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continue to attract and retain high quality personnel, which could negatively affect our ability to successfully develop and commercialize our product candidates and to grow our business and operations as currently contemplated.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of December 16, 2020, we had 68 full-time employees. We expect significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, clinical operations, manufacturing, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth and with developing sales, marketing and distribution infrastructure, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources.

Further, we currently rely, and for the foreseeable future will continue to rely, in substantial part on certain third-party contract organizations, advisors and consultants to provide certain services, including assuming substantial responsibilities for the conduct of our clinical trials and the manufacture of PRT543, PRT811 and PRT1419, or any future product candidates. We cannot assure you that the services of such third-party contract organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by our vendors or consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of PRT543, PRT811, PRT1419 or any future product candidates or otherwise advance our business. We cannot assure you that we will be able to properly manage our existing vendors or consultants or find other competent outside vendors and consultants on economically reasonable terms, or at all.

If we are not able to effectively manage growth and expand our organization, we may not be able to successfully implement the tasks necessary to further develop and commercialize PRT543, PRT811 or PRT1419, our other pipeline product candidates or any future product candidates and, accordingly, may not achieve our research, development and commercialization goals.

Our employees, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential commercial partners. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (i) FDA regulations or those of comparable foreign regulatory authorities, including those laws that require the reporting of true, complete and accurate information, (ii) manufacturing standards, (iii) federal and state health and data privacy, security, fraud and abuse, government price reporting, transparency reporting requirements, and other healthcare laws and regulations in the United States and abroad, (iv) sexual harassment and other workplace misconduct, or (v) laws that require the true, complete and accurate reporting of financial information or data. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation.

We have adopted a code of conduct applicable to all of our employees, as well as a disclosure program and other applicable policies and procedures, but it is not always possible to identify and deter employee misconduct,

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and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Our internal information technology systems, or those of our third-party CROs, CMOs, or other vendors, contractors or consultants, may fail or suffer security breaches, cyber-attacks, loss or leakage of data and other disruptions, which could result in a material disruption of our development programs, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability or otherwise adversely affecting our business.

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party CROs, CMOs, vendors, and other contractors and consultants who have access to our confidential information. Our internal information technology systems and infrastructure are also vulnerable to damage from natural disasters, terrorism, war, telecommunication and electrical failures. System failures or outages, including any potential disruptions due to significantly increased global demand on certain cloud-based systems during the COVID-19 situation, could compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting. Such failures could materially adversely affect our operating results and financial condition.

Despite the implementation of security measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third-party CROs, CMOs, vendors and other contractors and consultants are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, accidents by our employees or third party service providers, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, third-party CROs, CMOs, vendors, contractors, consultants, business partners and/or other third parties, or from cyber-attacks by malicious third parties (including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information), which may compromise our system infrastructure, or that of our third-party CROs, CMOs, vendors and other contractors and consultants, or lead to data leakage. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. The COVID-19 pandemic is generally increasing the attack surface available for exploitation, as more companies and individuals work online and work remotely, and as such, the risk of a cybersecurity incident potentially occurring, and our investment in risk mitigations against such an incident, is increasing. For example, there has been an increase in phishing and spam emails as well as social engineering attempts from “hackers” hoping to use the recent COVID-19 pandemic to their advantage. We may not be able to anticipate all types of security threats, nor may we be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile

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foreign governments or agencies. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or those of our third-party CROs, CMOs, vendors and other contractors and consultants, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of PRT543, PRT811, PRT1419 or any future product candidates could be delayed. Any breach, loss or compromise of clinical trial participant personal data may also subject us to civil fines and penalties, including under HIPAA, and other relevant state and federal privacy laws in the United States. The costs related to significant security breaches or disruptions could be material and exceed the limits of the cybersecurity insurance we maintain against such risks. If the information technology systems of our third-party CROs, CMOs, vendors and other contractors and consultants become subject to disruptions or security breaches, we may have insufficient recourse against such third parties and we may have to expend significant resources to mitigate the impact of such an event, and to develop and implement protections to prevent future events of this nature from occurring.

While we have not experienced any such system failure, accident or security breach to date, and believe that our data protection efforts and our investment in information technology reduce the likelihood of such incidents in the future, we cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems, or those of our third-party CROs, CMOs, vendors and other contractors and consultants, or other cyber incidents that could have a material adverse effect upon our reputation, business, operations or financial condition. For example, if such an event were to occur and cause interruptions in our operations, or those of our third-party CROs, CMOs, vendors and other contractors and consultants, it could result in a material disruption of our programs and the development of our product candidates could be delayed. In addition, the loss of clinical trial data for PRT543, PRT811, PRT1419 or any other product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or those of our third-party CROs, CMOs, vendors and other contractors and consultants, or security breaches could result in the loss, misappropriation and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business.

Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business.

We and any potential collaborators may be subject to federal, state and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. Depending on the facts and circumstances, we could be subject to criminal penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

International data protection laws, including Regulation 2016/679, known as the General Data Protection Regulation, or GDPR, may also apply to health-related and other personal information obtained outside of the

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United States. The GDPR went into effect on May 25, 2018. The GDPR introduced new data protection requirements in the EU, as well as potential fines for noncompliant companies of up to the greater of €20 million or 4% of annual global revenue. The regulation imposes numerous new requirements for the collection, use and disclosure of personal information, including more stringent requirements relating to consent and the information that must be shared with data subjects about how their personal information is used, the obligation to notify regulators and affected individuals of personal data breaches, extensive new internal privacy governance obligations and obligations to honor expanded rights of individuals in relation to their personal information (e.g., the right to access, correct and delete their data). In addition, the GDPR includes restrictions on cross-border data transfer. The GDPR will increase our responsibility and liability in relation to personal data that we process, and we may be required to put in place additional mechanisms to ensure compliance with the new EU data protection rules. In addition, the GDPR prohibits the transfer of personal data to countries outside of the European Economic Area, or EEA, such as the United States, which are not considered by the European Commission to provide an adequate level of data protection. Switzerland has adopted similar restrictions. Although there are legal mechanisms to allow for the transfer of personal data from the EEA and Switzerland to the United States, they are subject to pending legal challenges that, if successful, could invalidate these mechanisms, restrict our ability to process personal data of Europeans outside of Europe and adversely impact our business. For example, in July 2020, the European Courts of Justice invalidated the EU-U.S. Privacy Shield, which enabled the transfer of personal data from EU to the U.S. for companies that had self-certified to the Privacy Shield. On August 10, 2020, the U.S. Department of Commerce and the European Commission announced new discussions to evaluate the potential for an enhanced EU-U.S. Privacy Shield framework to comply with the July 16 judgment of the Court of Justice. While the Court of Justice upheld the use of other data transfer mechanisms, such as the Binding Corporate Rules, the decision has led to some uncertainty regarding the use of such mechanisms for data transfers to the United States, and the court made clear that reliance on Binding Corporate Rules alone may not necessarily be sufficient in all circumstances. Use of the data transfer mechanisms must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals. The European Data Protection Board issued additional guidance regarding the Court of Justice's decision on November 11, 2020 which imposes higher burdens on the use of data transfer mechanisms, such as the Binding Corporate Rules, for cross-border data transfers. To comply with this guidance, we may need to implement additional safeguards to further enhance the security of data transferred out of the European Economic Area, which could increase our compliance costs, expose us to further regulatory scrutiny and liability, and adversely affect our business. To the extent that we were to rely on Privacy Shield, we will not be able to do so in the future, which could increase our costs and our ability to efficiently process personal data from the EU.

Further, Brexit has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, while the Data Protection Act of 2018, that "implements" and complements the GDPR achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. During the period of "transition" (i.e., until December 31, 2020), EU law will continue to apply in the United Kingdom, including the GDPR, after which the GDPR will be converted into United Kingdom law. Beginning in 2021, the United Kingdom will be a "third country" under the GDPR. We may, however, incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

In addition, the state of California recently enacted the California Consumer Privacy Act, or CCPA, which creates new individual privacy rights for California consumers (as defined in the CCPA) and places increased privacy and security obligations on entities handling certain personal data of consumers or households. The CCPA requires covered companies to provide new disclosure to consumers about such companies' data collection, use and sharing practices, provide such consumers new ways to opt-out of certain sales or transfers of personal information, and provide consumers with additional causes of action. The CCPA went into effect on January 1, 2020 and became enforceable by the California Attorney General on July 1, 2020, along with related regulations which came into force on August 14, 2020 and may impact our business activities and exemplifies

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the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information. Additionally, although not effective until January 1, 2023, the California Privacy Rights Act (the “CPRA”), which expands upon the CCPA, was passed in the recent election on November 3, 2020. The CCPA gives (and the CPRA will give) California residents expanded privacy rights, including the right to request correction, access, and deletion of their personal information, the right to opt out of certain personal information sharing, and the right to receive detailed information about how their personal information is processed. The CCPA and CPRA provide for unlimited civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA and CPRA may increase our compliance costs and potential liability, particularly in the event of a data breach. Additionally, the CCPA has prompted a number of proposals in the U.S. for new federal and state-level privacy legislation that, if passed, could increase our potential liability, increase our compliance costs, and adversely affect our business.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with U.S. and international data protection laws and regulations could result in government enforcement actions (which could include civil, criminal, and administrative penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information. Claims that we have violated individuals’ privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time consuming to defend and could result in adverse publicity that could harm our business.

We or the third parties upon whom we depend may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our company is located in Delaware. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemic, including the COVID-19 pandemic, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize our facilities, or the manufacturing facilities of our third-party CMOs, may have a material and adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. For example, our operations are concentrated primarily on the east coast of the United States, and any adverse weather event or natural disaster, such as a hurricane or heavy snowstorm, could have a material adverse effect on a substantial portion of our operations. Extreme weather conditions or other natural disasters could further disrupt our operations, and have a material and adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our research facilities or the manufacturing facilities of our third-party CMOs, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities, or the manufacturing facilities of our third-party CMOs, are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption could have a material and adverse effect on our business, financial condition, results of operations and prospects.

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Changes in tax laws or regulations that are applied adversely to us may have a material adverse effect on our business, cash flow, financial condition or results of operations.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Cuts and Jobs Act, enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Cuts and Jobs Act may affect us, and certain aspects of the Tax Cuts and Jobs Act could be repealed or modified in future legislation. For example, the CARES Act modified certain provisions of the Tax Cuts and Jobs Act. In addition, it is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act, the CARES Act, or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Cuts and Jobs Act, the CARES Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history and do not expect to become profitable in the near future, and we may never achieve profitability. Unused losses incurred in taxable years beginning on or prior to December 31, 2017, will carry forward to offset future taxable income, if any, until such unused losses expire. Under the Tax Cuts and Jobs Act, as modified by the CARES Act, unused U.S. federal net operating losses generated in tax years beginning after December 31, 2017, will not expire and may be carried forward indefinitely but the deductibility of such federal net operating losses (particularly those generated in taxable years beginning after December 31, 2020) in taxable years beginning after December 31, 2020, is limited to 80% of current year taxable income. It is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act or the CARES Act. In addition, both our current and our future unused losses and other tax attributes may be subject to limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code) if we undergo, or have undergone, an “ownership change,” generally defined as a greater than 50 percentage point change (by value) in our equity ownership by certain stockholders over a three-year period. We have not completed a Section 382 study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since our formation due to the complexity and cost associated with such a study and the fact that there may be additional ownership changes in the future. As a result, our net operating loss carryforwards generated in taxable years beginning on or before December 31, 2017, may expire prior to being used, and the deductibility of our net operating loss carryforwards generated in taxable years beginning after December 31, 2017 in taxable years beginning after December 31, 2020, may be limited, and, if we undergo an ownership change (or if we previously underwent such an ownership change), our ability to use all of our pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset our post-change income or taxes may be limited. Similar provisions of state tax law may also apply to limit our use of accumulated state tax attributes. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, even if we attain profitability, we may be unable to use all or a material portion of our net operating losses and other tax attributes, which could adversely affect our future cash flows.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, businesses or assets and out-licensing or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near term or long-term

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expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations, systems and personnel of any acquired businesses with our operations, systems and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

Our portfolio of investments may be subject to market, interest and credit risk that may reduce its value.

The value of our investments may decline due to increases in interest rates, downgrades of the bonds and other securities included in our commercial money market account portfolio and instability in the global financial markets that reduces the liquidity of securities included in our portfolio. In addition, the COVID-19 pandemic has and may continue to adversely affect the financial markets in some or all countries worldwide. Each of these events may cause us to record charges to reduce the carrying value of our investment portfolio or sell investments for less than our acquisition cost. Although we attempt to mitigate these risks through diversification of our investments and continuous monitoring of our portfolio's overall risk profile, the value of our investments may nevertheless decline.

Risks Related to Intellectual Property

If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, third parties, including our competitors, could develop and commercialize products similar or identical to ours, and our ability to commercialize our product candidates successfully may be adversely affected.

Our success depends in large part on our ability to protect our proprietary technologies that we believe are important to our business, including pursuing, obtaining and maintaining patent protection in the United States and other countries intended to cover the compositions of matter of our product candidates, for example, PRT543, PRT811 and PRT1419, their methods of use, related technologies and other inventions that are important to our business. In addition to patent protection, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. If we do not adequately pursue, obtain, maintain, protect or enforce our intellectual property, third parties, including our competitors, may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability.

To protect our proprietary position, we have currently filed patent applications in the United States related to our product candidates that we consider important to our business, including patent applications relating to compositions of matter covering our compounds, the processes for manufacturing such compounds and use of such compounds in therapies. We have also filed patent applications abroad relating to PRT543 and PRT811.

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The patent application and approval process is expensive, time-consuming and complex. We may not be able to file, prosecute and maintain all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions. We also cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdictions. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, depending on the terms of any future license agreements to which we may become a party, we may not have the right to control the preparation, filing, and prosecution of patent applications, or to maintain the patents, covering technology licensed from third parties. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

Furthermore, the patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. The standards applied by the United States Patent and Trademark Office, or the USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. In addition, the determination of patent rights with respect to biological and pharmaceutical products commonly involves complex legal and factual questions, which have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Thus, we cannot offer any assurances about which, if any, patents will issue, the breadth of any such patents, whether any issued patents will be found invalid and unenforceable or will be threatened by third parties or whether any issued patents will effectively prevent others from commercializing competing technologies and product candidates. While we have filed patent applications covering aspects of our current product candidates, we currently have only one issued U.S. patent covering PRT543 that is expected to expire no earlier than August 9, 2038, and one issued U.S. patent covering PRT811 that is expected to expire no earlier than March 14, 2039. We do not yet have issued patents on all of our product candidates.

Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until at least one patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file or invent (prior to March 16, 2013) any patent application related to our product candidates. In addition, we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, collaborators, CROs, CMOs, hospitals, independent treatment centers, consultants, independent contractors, suppliers, advisors and other third parties; however, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Furthermore, if third parties have filed patent applications related to our product candidates or technology, we may not be able to obtain our own patent rights to those product candidates or technology.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. For example, we may be subject to a third-party pre-issuance submission of prior art to the USPTO or become involved in post-grant review procedures, oppositions, derivations, revocation, reexaminations, inter partes review or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party rights. Moreover, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant

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challenge proceedings, such as oppositions in a foreign patent office, that challenge priority of invention or other features of patentability. Such challenges may result in loss of exclusivity or in our patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products or limit the duration of the patent protection of our technology and products. Such challenges also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, our patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Moreover, some of our patents and patent applications may in the future be co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Our pending and future patent applications may not result in patents being issued that protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by valid and enforceable patents. Our competitors and other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors and other third parties may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors or other third parties may seek to market generic versions or "follow-on" versions of any approved products by submitting abbreviated new drug applications, or ANDAs, or new drug applications under Section 505(b)(2) of the FDCA, respectively, to the FDA during which they may claim that patents owned by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Furthermore, future patents may be subject to a reservation of rights by one or more third parties. For example, to the extent the research resulting in future patent rights or technologies is funded in the future in part by the U.S. government, the government could have certain rights in any resulting patents and technology, including a non-exclusive license authorizing the government to use the invention or to have others use the invention on its behalf for non-commercial purposes. If the U.S. government then decides to exercise these

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rights, it is not required to engage us as its contractor in connection with doing so. These rights may also permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government may also exercise its march-in rights if it determines that action is necessary because we failed to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such government-funded inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of aforementioned proprietary rights could harm our competitive position, business, financial condition, results of operations, and prospects.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or the Leahy-Smith Act, signed into law in September 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. For example, the Leahy-Smith Act allows third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, inter partes review, and derivation proceedings. In addition, the Leahy-Smith Act has transformed the U.S. patent system from a “first-to-invent” system to a “first-to-file” system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The first-to-file provisions, however, only became effective on March 16, 2013. It is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our or our future collaboration partners’ patent applications and the enforcement or defense of our or our future collaboration partners’ issued patents, all of which could harm our business, results of operations, financial condition and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may become involved in lawsuits or administrative disputes to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors and other third parties may infringe, misappropriate or otherwise violate our patents, trademarks, copyrights, trade secrets or other intellectual property. To counter infringement, misappropriation or

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other violations, we may be required to file infringement, misappropriation or other violation claims, which can be expensive and time consuming and divert the time and attention of our management and business and scientific personnel. In addition, many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can.

Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their patents or their other intellectual property, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In patent litigation in the United States, counterclaims challenging the validity, enforceability or scope of asserted patents are commonplace. Similarly, third parties may initiate legal proceedings against us seeking a declaration that certain of our intellectual property is non-infringed, invalid or unenforceable. The outcome of any such proceeding is generally unpredictable.

In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. If a defendant were to prevail on a legal assertion of invalidity or unenforceability of our patents covering one of our product candidates, we could lose at least a part, and perhaps all, of the patent protection covering such a product candidate. Competing drugs may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit, alleging our infringement of a competitor's patents, we could be prevented from marketing our drugs in one or more foreign countries. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Furthermore, third parties may also raise invalidity or unenforceability claims before administrative bodies in the United States or foreign authorities, even outside the context of litigation. Such mechanisms include re-examination, inter partes review, post-grant review, interference proceedings, derivation proceedings and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation, cancellation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or written description. Grounds for an unenforceability assertion could be an allegation that someone connected with the prosecution of the patent withheld relevant

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information from the USPTO, or made a misleading statement, during prosecution of the patent. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we, our licensors, our patent counsel and the patent examiner were unaware during prosecution. Moreover, it is possible that prior art may exist that we are aware of but do not believe is relevant to our current or future patents, but that could nevertheless be determined to render our patents invalid. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates. Any such loss of patent protection could have a material adverse impact on our business, financial condition, results of operations and prospects.

We may not be able to effectively protect or enforce our intellectual property and proprietary rights throughout the world.

Filing, prosecuting and defending patents with respect to our product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. The requirements for patentability may differ in certain countries, particularly in developing countries. In addition, any future intellectual property license agreements may not always include worldwide rights. Consequently, competitors and other third parties may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we may obtain patent protection, but where patent enforcement is not as strong as that in the United States and where our ability to enforce our patents to stop infringing activities may be inadequate. These products may compete with our products in such territories and in jurisdictions where we do not have any patent rights or where any future patent claims or other intellectual property or proprietary rights may not be effective or sufficient to prevent them from competing with us, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Moreover, our ability to protect and enforce our intellectual property and proprietary rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, the laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property and proprietary rights in certain foreign jurisdictions. The legal systems of some countries, including, for example, India, China and other developing countries, do not view favorably the enforcement of patents and other intellectual property or proprietary rights, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement, misappropriation or other violation of our patents or other intellectual property or proprietary rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business, could put our patents, trademarks or other intellectual property and proprietary rights at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property and proprietary rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property and proprietary rights in such countries may be inadequate.

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If we are sued for infringing, misappropriating or otherwise violating intellectual property or proprietary rights of third parties, such litigation or disputes could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and other proprietary rights of third parties. If any third-party patents, patent applications or other proprietary rights are found to cover our product candidates or any related companion diagnostics or their compositions, methods of use or manufacturing, we may be required to pay damages, which could be substantial, and we would not be free to manufacture or market our product candidates or to do so without obtaining a license, which may not be available on commercially reasonable terms, or at all.

We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property or proprietary rights with respect to our product candidates and technologies we use in our business. Our competitors or other third parties may assert infringement claims against us, alleging that our product candidates are covered by their patents. We cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our product candidates. If a patent holder believes our product candidate infringes its patent rights, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property or proprietary rights with respect to our product candidates, including interference proceedings before the USPTO. Third parties may assert infringement, misappropriation or other claims against us based on existing or future intellectual property or proprietary rights. The outcome of intellectual property litigation and other disputes is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of using or manufacturing products. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods of use, manufacturing or other applicable activities either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be successful in doing so. However, proving invalidity or unenforceability is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, or enforceability. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and business and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property or proprietary rights and we are unsuccessful in demonstrating that such intellectual property or proprietary rights are invalid or unenforceable, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on

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non-exclusive terms, thereby giving our competitors and other third parties access to the same technologies licensed to us. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed such third-party patent rights. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

We may be subject to claims by third parties asserting that our employees or consultants or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Some of our employees and consultants are currently or have been previously employed at universities or at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. These employees and consultants may have executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such other current or previous employment. Although we try to ensure that our employees and consultants do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of third parties. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property or personnel or sustain damages. Such intellectual property could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management. Any of the foregoing would have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. In addition, such agreements may not be self-executing such that the intellectual property subject to such agreements may not be assigned to us without additional assignments being executed, and we may fail to obtain such assignments. In addition, such agreements may be breached. In addition, we have multiple sponsored research agreements relating to our lead product candidates with various academic institutions. Some of these academic institutions may not have intellectual property assignments or similar agreements with their employees and consultants, which may result in claims by or against us related to ownership of any intellectual property. Accordingly, we may be forced to bring claims against third parties, or defend claims that they may bring against us to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

Rights to improvements to our product candidates may be held by third parties.

In the course of testing our product candidates, we have entered into agreements with third parties to conduct clinical testing, which provide that improvements to our product candidates may be owned solely by a party or jointly between the parties. If we determine that rights to such improvements owned solely by a third party are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to use the improvements and continue developing,

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manufacturing or marketing the product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby giving our competitors and other third parties access to the same technologies licensed to us. Failure to obtain a license on commercially reasonable terms or at all, or to obtain an exclusive license, could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. If we determine that rights to improvements jointly owned between us and a third party are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain an exclusive license from such third party. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such improvements, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our intellectual property in order to enforce such intellectual property against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

The term of our patents may be inadequate to protect our competitive position on our products.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Depending upon the timing, duration and other factors relating to any FDA marketing approval we receive for any of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Action of 1984, or the Hatch-Waxman Amendments. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Hatch-Waxman Amendments permit a patent term extension of up to five years beyond the normal expiration of the patent, limited to the approved indication (or any additional indications approved during the period of extension), as compensation for patent term lost to the regulatory review process during which the sponsor was unable to commercially market its new product. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to an approved drug is eligible for the extension and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended, and the application for the extension must be submitted prior to the expiration of the patent. However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available for our patents, may refuse to grant extensions to our patents, or may grant more limited extensions than we request. We may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors and other third parties may be able to obtain approval of competing products following our patent expiration and take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. Any of the foregoing would have a material adverse effect on our business, financial condition, results of operations and prospects.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by governmental patent offices, and our patent protection could be reduced or eliminated for noncompliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on any issued patent are due to be paid to the USPTO and patent offices in foreign countries in several stages over the lifetime of the patent. The USPTO and patent offices in foreign countries require compliance with a number of procedural, documentary, fee payment and other requirements during the patent application process. In the future, we may rely on licensing partners to pay these fees due to U.S. and non-U.S. patent agencies and to

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comply with these other requirements with respect to any future licensed patents and patent applications. While an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of a patent or patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors and other third parties might be able to enter the market with similar or identical products of technology, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.

We rely on proprietary know-how and trade secret protection and confidentiality agreements to protect proprietary know-how or trade secrets that are not patentable or that we elect not to patent. We seek to protect our trade secrets and proprietary know-how in part by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, consultants, independent contractors, advisors, CMOs, CROs, hospitals, independent treatment centers, suppliers, collaborators and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary know-how. Additionally, our confidentiality agreements and other contractual protections may not be adequate to protect our intellectual property from unauthorized disclosure, third-party infringement or misappropriation. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts in the United States and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our business, financial condition, results of operations and prospects our business and competitive position could be materially harmed.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products similar to any product candidates we may develop or utilize similarly related technologies that are not covered by the claims of the patents that we may license or may own in the future;
- we, or any future license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or any future license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating any of our owned or licensed intellectual property rights;

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- it is possible that our pending patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Our Common Stock and This Offering

An active and liquid trading market for our common stock may never be sustained. As a result, you may not be able to resell your shares of common stock at or above the public offering price.

An active trading market for our common stock may never be sustained following this offering. The market value of our common stock may decrease from the public offering price. As a result of these and other factors, you may be unable to resell your shares of our common stock at or above the public offering price. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair market value of your shares. Furthermore, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic collaborations or acquire companies or products by using our shares of common stock as consideration.

Our quarterly operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expense related to the planned and ongoing development of our product candidates or future development programs, including scale-up CMC expenses;
- results of clinical trials, or the addition or termination of future preclinical or clinical trials or funding support by us, or future collaborators or licensing partners;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under existing or future arrangements or the termination or modification of any such existing or future arrangements;
- any intellectual property infringement lawsuit or opposition, interference or cancellation proceeding in which we may become involved;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- if any of our product candidates receives regulatory approval, the terms of such approval and market acceptance and demand for such product candidates;

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- regulatory developments affecting our product candidates or those of our competitors; and
- changes in general market and economic conditions, such as due to the recent COVID-19 pandemic.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our common stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

The market price of our common stock is likely to be highly volatile, which could result in substantial losses for purchasers of our common stock.

The market price of our common stock has been highly volatile since our IPO and has ranged from \$23.69 to \$82.64 per share. The market price of our common stock is likely to continue to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid in this offering. The market price for our common stock may be influenced by many factors, including the other risks described in this section of the prospectus and the following:

- enrollment or results of clinical trials of our product candidates, or those of our competitors or our future collaborators, or changes in the development status of our product candidates;
- regulatory or legal developments in the United States and other countries, especially changes in laws or regulations applicable to our product candidates;
- the success of competitive products or technologies;
- introductions and announcements of new products by us, our future commercialization partners, or our competitors, and the timing of these introductions or announcements;
- actions taken by regulatory agencies with respect to our products, clinical studies, manufacturing process or sales and marketing terms;
- actual or anticipated variations in our financial results or those of companies that are perceived to be similar to us;
- the success of our efforts to acquire or in-license additional technologies, products or product candidates;
- developments concerning any future collaborations, including but not limited to those with development and commercialization partners;
- market conditions in the pharmaceutical and biotechnology sectors;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures or capital commitments;
- developments or disputes concerning patents or other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our product candidates and products;
- our ability or inability to raise additional capital and the terms on which we raise it;
- the recruitment or departure of key personnel;
- changes in the structure of healthcare payment systems;
- actual or anticipated changes in earnings estimates or changes in stock market analyst recommendations regarding our common stock, other comparable companies or our industry generally;

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- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- announcement and expectation of additional financing efforts;
- speculation in the press or investment community;
- share price and fluctuations of trading volume of our common stock;
- sales of our common stock by us, insiders or our stockholders;
- the concentrated ownership of our common stock;
- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;
- natural disasters and other calamities; and
- general economic, industry and market conditions, or other events or factors, many of which are beyond our control, such as the recent COVID-19 pandemic.

In addition, the stock market in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme price and volume fluctuations that have been often unrelated or disproportionate to the operating performance of the issuer. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this "Risk Factors" section, could have a dramatic and adverse impact on the market price of our common stock.

In the past, securities class action litigation has often been brought against public companies following declines in the market price of their securities. This risk is especially relevant for biopharmaceutical companies, which have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and our resources, which could harm our business.

You will experience immediate and substantial dilution as a result of this offering and may experience additional dilution in the future.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of _____ shares of our common stock are sold at a price of \$ _____ per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of \$ _____ per share. For a more detailed discussion of the foregoing, see the section entitled "Dilution" below. To the extent outstanding stock options are exercised, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

Management will have broad discretion as to the use of proceeds from this offering and we may use the net proceeds in ways with which you may disagree.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled "Use of Proceeds," and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this

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offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering to fund research, clinical and process development and manufacturing of our product candidates, working capital, capital expenditures and other general corporate purposes. The failure by our management to apply these funds effectively could harm our business. Pending their use, we plan to invest the net proceeds from this offering in short-term or long-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

A sale of a substantial number of shares of our common stock may cause the price of our common stock to decline.

Based on shares outstanding as of September 30, 2020, upon completion of this offering, we will have outstanding a total of _____ shares of common stock and non-voting common stock. In connection with this offering, each of our directors and officers and certain of our stockholders will enter into lock-up agreements with the underwriters that restrict their ability to sell or transfer their shares. In connection with our IPO, each of our officers, directors and substantially all of our stockholders entered into lock-up agreements with the underwriters that restrict their ability to sell or transfer their shares. The lock-up agreements pertaining to this offering will expire 90 days from the date of this prospectus and the lock-up agreements pertaining to our IPO will expire 180 days from the date of effectiveness of our IPO registration statement. However, our underwriters may, in their sole discretion, permit our officers, directors and other stockholders who are subject to the contractual lock-ups to sell shares prior to the expiration of the lock-up agreements. See “Underwriters” for a description of these lock-up agreements.

We cannot predict what effect, if any, sales of our shares in the public market or the availability of shares for sale will have on the market price of our common stock. However, future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of outstanding options, or the perception that such sales may occur, could adversely affect the market price of our common stock.

We also expect that significant additional capital may be needed in the future to continue our planned operations, including conducting our planned clinical trials, manufacturing and commercialization efforts, expanded research and development activities and costs associated with operating as a public company. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

Our principal stockholders and management own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.

As of November 30, 2020, prior to this offering, our executive officers, directors, beneficial owners of 5% or more of our capital stock and their respective affiliates beneficially owned approximately 73.4% of our common stock. Upon the completion of this offering, that same group will hold _____ % of our outstanding voting stock (assuming no exercise of the underwriters’ option to purchase additional shares, no exercise of our outstanding warrant or options and no purchases of shares in this offering by any of this group). The voting power of this group may increase to the extent they convert shares of non-voting common stock they hold into common stock.

This group of stockholders have the ability to control us through this ownership position and are able to determine all matters requiring stockholder approval. For example, these stockholders are able to control elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this

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group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

Participation in this offering by our existing stockholders or their affiliated entities may reduce the public float for our common stock.

To the extent our existing stockholders who are our affiliates or their affiliated entities participate in this offering, such purchases would reduce the non-affiliate public float of our common stock after this offering, which is the number of shares of common stock that are not held by our officers, directors and affiliated stockholders. A reduction in the public float could reduce the number of shares of common stock that can be traded at any given time, which could adversely impact the liquidity of our common stock and depress the price at which you may be able to sell common stock purchased in this offering.

The dual class structure of our common stock may limit your ability to influence corporate matters and may limit your visibility with respect to certain transactions.

The dual class structure of our common stock may limit your ability to influence corporate matters. Holders of our common stock are entitled to one vote per share, while holders of our non-voting common stock are not entitled to any votes. Nonetheless, each share of our non-voting common stock may be converted at any time into one share of our common stock at the option of its holder by providing written notice to us, subject to the limitations provided for in our restated certificate of incorporation. Consequently, if holders of our non-voting common stock exercise their option to make this conversion, this will have the effect of increasing the relative voting power of those prior holders of our non-voting common stock, and correspondingly decreasing the voting power of the holders of our common stock, which may limit your ability to influence corporate matters. For example, at November 30, 2020, the common stock will have 100% of the voting power, but if the holders of non-voting common stock were to convert all of their shares into common stock, the prior common stock would have 74.6% of the voting power, and the former non-voting common stock would represent 25.4% of the voting power. Additionally, stockholders who hold, in the aggregate, more than 10% of our common stock and non-voting common stock, but 10% or less of our common stock, and are not otherwise an insider of the company, may not be required to report changes in their ownership due to transactions in our non-voting common stock pursuant to Section 16(a) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and may not be subject to the short-swing profit provisions of Section 16(b) of the Exchange Act.

We are an “emerging growth company” and a “smaller reporting company” and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies or smaller reporting companies will make our common stock less attractive to investors.

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including (i) not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, (ii) reduced disclosure obligations regarding executive compensation in this prospectus as well as our periodic reports and proxy statements and (iii) exemptions from the requirements of holding nonbinding advisory stockholder votes on executive compensation and stockholder approval of any golden parachute payments not approved previously. In addition, as an emerging growth company, we are only required to provide two years of audited financial statements and two years of selected financial data in this prospectus.

We could be an emerging growth company until December 31, 2025, although circumstances could cause us to lose that status earlier, including if we are deemed to be a “large accelerated filer,” which occurs when the market value of our common stock that is held by non-affiliates equals or exceeds \$700 million as of the prior

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June 30, or if we have total annual gross revenue of \$1.07 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31, or if we issue more than \$1.0 billion in non-convertible debt during any three-year period before that time, in which case we would no longer be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a “smaller reporting company,” which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, if our revenues remain less than \$100.0 million, and reduced disclosure obligations regarding executive compensation in this prospectus as well as our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to take advantage of the benefits of this extended transition period. Our financial statements may therefore not be comparable to those of companies that comply with such new or revised accounting standards. Until the date that we are no longer an “emerging growth company” or affirmatively and irrevocably opt out of the exemption provided by Section 7(a)(2)(B) of the Securities Act, upon issuance of a new or revised accounting standard that applies to our financial statements and that has a different effective date for public and private companies, we will disclose the date on which adoption is required for non-emerging growth companies and the date on which we will adopt the recently issued accounting standard.

We are also a “smaller reporting company,” meaning that the market value of our stock held by non-affiliates is less than \$700.0 million and our annual revenue is less than \$100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than \$250.0 million or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than \$700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

Anti-takeover provisions in our charter documents and under Delaware law could prevent or delay an acquisition of us, which may be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Our restated certificate of incorporation and our restated bylaws contain provisions that could delay or prevent a change in control of our company. These provisions could also make it difficult for stockholders to elect directors who are not nominated by current members of our board of directors or take other corporate actions, including effecting changes in our management. These provisions:

- establish a classified board of directors so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed “for cause” and only with the approval of two-thirds of our stockholders;
- require super-majority voting to amend some provisions in our restated certificate of incorporation and restated bylaws;
- authorize the issuance of “blank check” preferred stock that our board could use to implement a stockholder rights plan;

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- eliminate the ability of our stockholders to call special meetings of stockholders;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- prohibit cumulative voting; and
- establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings.

In addition, Section 203 of the Delaware General Corporation Law, or DGCL, may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15% or more of our common stock.

The exclusive forum provision in our organizational documents may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims.

Our restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our restated certificate of incorporation, or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision does not apply to suits brought to enforce a duty or liability created by the Exchange Act. It could apply, however, to a suit that falls within one or more of the categories enumerated in the exclusive forum provision.

This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations and financial condition.

Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all claims brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. Our restated bylaws will provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or a Federal Forum Provision. Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court.

Section 27 of the Exchange Act creates exclusive federal jurisdiction over all claims brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. In addition, neither the exclusive forum provision nor the Federal Forum Provision applies to suits brought to enforce any duty or liability created by the Exchange Act. Accordingly, actions by our stockholders to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder must be brought in federal court.

Our stockholders will not be deemed to have waived our compliance with the federal securities laws and the regulations promulgated thereunder.

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Any person or entity purchasing or otherwise acquiring or holding any interest in any of our securities shall be deemed to have notice of and consented to our exclusive forum provisions, including the Federal Forum Provision. These provisions may limit a stockholders' ability to bring a claim in a judicial forum of their choosing for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees.

We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an emerging growth company, we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, we expect these rules and regulations to substantially increase our legal and financial compliance costs and to make some activities more time consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain sufficient coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. The increased costs may require us to reduce costs in other areas of our business or increase the prices of our products once commercialized. Moreover, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

We are not currently required to comply with the SEC's rules that implement Section 404 of the Sarbanes-Oxley Act, and are therefore not required to make a formal assessment of the effectiveness of our internal control over financial reporting for that purpose. Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In addition, for as long as we are a smaller reporting company with less than \$100 million in annual revenue, we would be exempt from the requirement to obtain an external audit on the effectiveness of internal control over financial reporting provided in Section 404(b) of the Sarbanes-Oxley Act. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. This process will be time-consuming, costly and complicated. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. In addition, if we are not able to continue to meet these requirements, we may not be able to remain listed on the Nasdaq Global Select Market.

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Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

General Risk Factors

If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our stock, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If no or few securities or industry analysts commence coverage of us, the trading price for our common stock could be impacted negatively. In the event we obtain securities or industry analyst coverage, if any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our preclinical studies and clinical trials and operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of such analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause a decline in our stock price or trading volume.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. For example, our directors or executive officers could inadvertently fail to disclose a new relationship or arrangement causing us to fail to make any related party transaction disclosures. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected. In addition, we do not have a risk management program or processes or procedures for identifying and addressing risks to our business in other areas.

We may be subject to securities litigation, which is expensive and could divert management attention.

The market price of our common stock may be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the sections entitled “Prospectus Summary,” “Risk Factors,” “Use of Proceeds,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and “Business,” contains forward-looking statements about us and our industry. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “intend,” “could,” “would,” “project,” “plan,” “expect” and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus include, among other things, statements about:

- our plans to develop and commercialize our product candidates, PRT543, PRT811 and PRT 1419, for the treatment of solid tumors and myeloid malignancies;
- our ability to obtain funding for our operations, including funding necessary to complete further discovery, development and commercialization of our product candidates;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates, PRT543, PRT811 and PRT1419, as well as our other product candidates;
- future agreements with third parties in connection with the commercialization of our product candidates;
- the success, cost and timing of our product candidate development activities and planned clinical trials;
- the outbreak of the coronavirus, or COVID-19, pandemic and its potentially material adverse impact on our business, the macroeconomy, and the execution of our clinical trials;
- the rate and degree of market acceptance and clinical utility of our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the success of competing therapies that are or may become available;
- our ability to attract and retain key management and technical personnel;
- our expectations regarding our ability to obtain, maintain and enforce intellectual property protection for our product candidates;
- our use of the net proceeds from this offering; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in “Risk Factors” and elsewhere in this prospectus. Moreover, we operate in a competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this prospectus may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this prospectus to conform these statements to actual results or to changes in our expectations, except as required by law.

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You should read this prospectus and the documents that we reference in this prospectus and have filed with the Securities and Exchange Commission, or SEC, as exhibits to the registration statement of which this prospectus is a part with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and you are cautioned not to unduly rely upon these statements.

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MARKET AND INDUSTRY DATA

This prospectus contains estimates and other statistical data made by independent parties and by us relating to our industry and the markets in which we operate, including our general expectations and market position, market opportunity, the incidence of certain medical conditions and other industry data. These data, to the extent they contain estimates or projections, involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates or projections. Industry publications and other reports we have obtained from independent parties generally state that the data contained in these publications or other reports have been obtained in good faith or from sources considered to be reliable, but they do not guarantee the accuracy or completeness of such data. The industry in which we operate is subject to risks and uncertainties due to a variety of factors, including those described in the section entitled “Risk Factors.” These and other factors could cause results to differ materially from those expressed in these publications and reports.

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USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately \$ _____ million from the sale of _____ shares of common stock in this offering, or approximately \$ _____ million if the underwriters exercise their option to purchase additional shares in full, based on an assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Each \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, would increase (decrease) the net proceeds to us from this offering by \$ _____ million, assuming the number of shares offered, as set forth on the cover of this prospectus, remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 1,000,000 shares in the number of shares of common stock offered would increase (decrease) the net proceeds that we receive from this offering by \$ _____ million, assuming the assumed public offering price remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We currently intend to use the net proceeds we receive from this offering, as follows:

- approximately \$ _____ million to \$ _____ million to advance the clinical development of PRT543, including to completion of our ongoing Phase 1 clinical trial in patients with solid tumors and hematological malignancies and, subject to feedback from the FDA, to enable registration readiness and scale up of drug supply and to conduct potential Phase 2 clinical trials in one or more targeted indications;
- approximately \$ _____ million to \$ _____ million to advance the clinical development of PRT811, including to completion of our ongoing Phase 1 clinical trial in patients with advanced solid tumors and, subject to feedback from the FDA, to enable registration readiness and scale up of drug supply and to conduct potential Phase 2 clinical trials in one or more indications;
- approximately \$ _____ million to \$ _____ million to advance the clinical development of PRT1419, including to completion of our ongoing Phase 1 clinical trials in patients with R/R high risk MF or MDS and R/R NHL or MM or solid tumors and, subject to feedback from the FDA, we may to conduct initiate potential Phase 2 clinical trials in one or more targeted indications;
- approximately \$ _____ million to \$ _____ million to advance the preclinical and clinical development of PRT2527, including to completion of our planned Phase 1 clinical trial in solid tumors and/or hematological malignancies;
- approximately \$ _____ million to \$ _____ million to fund further development of our preclinical programs towards IND filings and/or into clinical trials; and
- any remaining amounts to fund working capital and general corporate purposes.

Based on our planned use of the net proceeds, we estimate such funds, together with our existing cash and cash equivalents, will be sufficient for us to fund our operating expenses and capital expenditure requirements into _____. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we expect.

The expected use of the net proceeds from the offering represents our intentions based upon our current plans and business conditions. The amounts we actually expend in these areas, and the timing thereof, may vary significantly from our current intentions and will depend on a number of factors, including the success of research and product development efforts, cash generated from future operations and actual expenses to operate our business. We may use a portion of the net proceeds for the acquisition of, or investment in, businesses that complement our business, although we have no present commitments or agreements.

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The amounts and timing of our preclinical and clinical expenditures and the extent of preclinical and clinical development may vary significantly depending on numerous factors, including the status, results and timing of our current preclinical studies and clinical trials, and the preclinical studies and clinical trials which we may commence in the future, the product approval process with the FDA and other regulatory agencies, any new collaborations we may enter into with third parties, any unforeseen cash needs and other factors described under “Risk Factors” in this prospectus. As a result, we cannot predict with any certainty all of the particular uses for the net proceeds or the amounts that we will actually spend on the uses set forth above. Accordingly, our management will have broad discretion in the application of the net proceeds, and investors will be relying on the judgment of our management regarding the application of the net proceeds of this offering.

The expected net proceeds of this offering will not be sufficient for us to fund any of our product candidates through regulatory approval, and we will need to raise substantial additional capital to complete the development and commercialization of our product candidates.

Pending the uses described above, we intend to invest the net proceeds from this offering in short term, investment-grade interest-bearing securities such as money market accounts, certificates of deposit, commercial paper and guaranteed obligations of the U.S. government.

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DIVIDEND POLICY

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any cash dividends on our common stock or non-voting common stock in the foreseeable future.

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CAPITALIZATION

The following table sets forth our cash and cash equivalents and capitalization as of September 30, 2020 on:

- an actual basis; and
- an as adjusted basis, giving effect to the sale of _____ shares of common stock in this offering, at an assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The pro forma as adjusted information set forth in the table below is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering as determined at pricing.

You should read this table together with the sections titled “Selected Financial Data” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes, each included elsewhere in this prospectus.

	As of September 30, 2020	
	Actual	As Adjusted(1)
	(in thousands, except share and per share data)	
Cash and cash equivalents	\$ 234,792	
Stockholders’ equity:		
Preferred stock, \$0.0001 par value: 10,000,000 shares authorized, no shares issued or outstanding, actual; actual and as adjusted	—	
Voting common stock, \$0.0001 par value: 487,149,741 shares authorized, actual and as adjusted: 32,593,010 shares issued and outstanding, actual; _____ shares issued and outstanding, as adjusted	3	
Non-voting common stock, \$0.0001 par value: 12,850,259 shares authorized, 11,110,371 shares issued and outstanding, actual and as adjusted	1	
Additional paid-in capital	316,479	
Accumulated deficit	(88,176)	
Total stockholders’ equity	228,307	
Total capitalization	\$ 228,307	

- (1) As adjusted amounts reflect the sale of _____ shares of our common stock by us in this offering at the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, after deducting the estimated underwriting discounts and commissions and estimated offering expenses. A \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, would increase (decrease) the as adjusted amount of each of cash and cash equivalents, additional paid-in capital, total stockholders’ equity and total capitalization by \$ _____ million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 1,000,000 in the number of shares offered by us in this offering would increase (decrease) the as adjusted amount of each of cash and cash equivalents, working capital, total assets, additional paid-in capital, total stockholders’ equity and total capitalization by \$ _____ million, assuming the assumed public offering price remains the same and after deducting estimated underwriting discounts commissions and estimated offering expenses payable by us.

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The table above excludes the following:

- 6,649,882 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2020 under our 2016 Stock Incentive Plan, or the 2016 Plan, and our 2020 Equity Incentive Plan, or the 2020 Plan, with an average exercise price of \$7.00 per share;
- 127,000 shares of common stock issuable upon the exercise of stock options granted after September 30, 2020 under the 2020 Plan with an exercise price of \$52.90; and
- 5,197,407 shares of common stock reserved for future issuance under our stock-based compensation plans, consisting of (i) 4,677,407 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 520,000 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan, or the ESPP. Our 2020 Plan and ESPP also provide for automatic annual increases in the number of shares reserved under the plans each year, as more fully described in “Executive Compensation—Equity Compensation Plans and Other Benefit Plans.”

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DILUTION

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the amount per share paid by purchasers of shares of common stock in this offering and the as adjusted net tangible book value per share of common stock immediately after this offering.

Net tangible book value per share is determined by dividing our total tangible assets less our total liabilities by the number of shares of common stock outstanding. Our net tangible book value as of September 30, 2020 was \$228.3 million, or \$5.22 per share, based on 43,703,381 shares of common stock and non-voting common stock (of which 11,110,371 shares are non-voting common stock) outstanding as of that date.

Net tangible book value dilution per share to new investors in this offering represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the as adjusted net tangible book value per share of common stock immediately after completion of this offering. After giving effect to our sale in this offering of _____ shares of our common stock at an assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2020 would have been approximately \$ _____ million, or \$ _____ per share of our common stock. This represents an immediate increase in adjusted net tangible book value of \$ _____ per share to our existing stockholders and an immediate dilution in net tangible book value of \$ _____ per share to investors in this offering, as illustrated in the following table:

Assumed public offering price, per share	\$
Net tangible book value per share as of September 30, 2020	\$ 5.22
Increase in net tangible book value per share attributable to new investors in this offering	
As adjusted net tangible book value per share after this offering	
Dilution per share to new investors in this offering	\$

Each \$1.00 increase (decrease) in the assumed public offering price of \$ _____ per share, which is the last reported sale price of our common stock on the Nasdaq Global Select Market on _____, 2021, would increase (decrease) the as adjusted amount of each of cash and cash equivalents, working capital, total assets and total stockholders' equity by \$ _____ million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, an increase (decrease) of 1,000,000 in the number of shares offered by us in this offering would increase (decrease) the as adjusted amount of each of cash and cash equivalents, working capital, total assets and total stockholders' equity by \$ _____ million, assuming the assumed public offering price remains the same and after deducting estimated underwriting discounts commissions and estimated offering expenses payable by us.

If the underwriters exercise their option in full to purchase additional shares, the as adjusted net tangible book value per share after this offering would be \$ _____ per share, the increase in as adjusted net tangible book value per share to existing stockholders would be \$ _____ per share and the dilution to new investors in this offering would be \$ _____ per share.

In addition, to the extent that any outstanding options are exercised, investors in this offering will experience further dilution.

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The number of shares of our common stock to be outstanding after this offering is based on 43,703,381 shares of common stock and non-voting common stock (of which 11,110,371 shares are non-voting common stock) immediately prior to the completion of this offering, and excludes:

- 6,649,882 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2020 under our 2016 Plan and our 2020 Plan, with an average exercise price of \$7.00 per share;
- 127,000 shares of common stock issuable upon the exercise of stock options granted after September 30, 2020 under the 2020 Plan with an exercise price of \$52.90; and
- 5,197,407 shares of common stock reserved for future issuance under our stock-based compensation plans, consisting of (i) 4,677,407 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 520,000 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan, or the ESPP. Our 2020 Plan and ESPP also provide for automatic annual increases in the number of shares reserved under the plans each year, as more fully described in “Executive Compensation—Equity Compensation Plans and Other Benefit Plans.”

To the extent that these outstanding stock options are exercised, new stock options are issued or we issue additional shares of common stock in the future, there will be further dilution to new investors. In addition, we may choose to raise additional capital because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

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SELECTED FINANCIAL DATA

The following tables set forth our selected statements of operations and balance sheet data. The selected statement of operations data presented below for the years ended December 31, 2018 and 2019 and balance sheet data as of December 31, 2018 and 2019 are derived from our audited financial statements included elsewhere in this prospectus. The selected statement of operations data for the nine months ended September 30, 2019 and 2020 and balance sheet data as of September 30, 2020 are derived from our unaudited interim financial statements included elsewhere in this prospectus. The unaudited interim financial statements, in management's opinion, have been prepared on the same basis as the audited financial statements and the related notes included elsewhere in this prospectus, and include all adjustments, consisting only of normal recurring adjustments, that management considers necessary for a fair presentation of the information for the periods presented. The following selected financial data below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes included elsewhere in this prospectus. Our historical results are not necessarily indicative of the results that may be expected in any future period and the results for the nine months ended September 30, 2020 are not necessarily indicative of the results that may be expected for the year ended December 31, 2020. The selected financial data in this section are not intended to replace the financial statements and are qualified in their entirety by the financial statements and related notes included elsewhere in this prospectus.

(in thousands, except share and per share data)	Year ended December 31,		Nine months ended September 30,	
	2018	2019	2019	2020
Statement of Operations Data:				
Operating expenses:				
Research and development	\$ 12,621	\$ 24,279	\$ 15,430	\$ 33,605
General and administrative	2,354	3,830	2,584	5,712
Total operating expenses	14,975	28,109	18,014	39,317
Loss from operations	(14,975)	(28,109)	(18,014)	(39,317)
Other income, net	295	539	483	1,638
Net loss	\$ (14,680)	\$ (27,570)	\$ (17,531)	\$ (37,679)
Per share information:				
Net loss per share of common stock, basic and diluted ⁽¹⁾	\$ (10.46)	\$ (16.52)	\$ (10.80)	\$ (15.83)
Weighted average common shares outstanding, basic and diluted ⁽¹⁾	1,402,928	1,668,549	1,622,546	2,380,100

(1) See Note 3 to our financial statements included elsewhere in this prospectus for a description of how we compute net loss per share of common stock, basic and diluted and the weighted average shares outstanding used in the computation of these per share amounts.

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(in thousands)	As of December 31,		As of
	2018	2019	September 30, 2020
Balance Sheet Data:			
Cash and cash equivalents	\$ 15,595	\$ 18,879	\$ 234,792
Working capital ⁽¹⁾	13,148	15,389	226,702
Total assets	16,406	21,871	239,681
Total convertible preferred stock	36,595	66,443	—
Accumulated deficit	(22,927)	(50,497)	(88,176)
Total stockholders' (deficit) equity	(22,693)	(49,412)	367,107

(1) We define working capital as current assets less current liabilities. See our financial statements and related notes appearing at the end of this prospectus for further details regarding our current assets and current liabilities.

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**MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND
RESULTS OF OPERATIONS**

You should read the following discussion and analysis of our financial condition and results of operations together with the section titled "Selected Financial Data" in this prospectus and our financial statements and the related notes and other financial information included elsewhere in this prospectus. Some of the information contained in this discussion and analysis, including information with respect to our plans and strategy for our business, and the potential impacts of the ongoing COVID-19 pandemic, contains forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in this prospectus for a discussion of important factors that could cause actual results to differ materially from the results described below. Please also see the section entitled "Special Note Regarding Forward-Looking Statements."

Overview

We are a clinical-stage precision oncology company focused on discovering and developing small molecule therapies optimized to target the key driver mechanisms in cancers with high unmet need. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our target class- and technology platform-agnostic approach, we have built an efficient, fully-integrated drug discovery engine to identify compelling biological targets and create new chemical entities, or NCEs, that we rapidly advance into clinical development. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our rapid progress in creating a wholly-owned, internally developed pipeline. Since our inception in 2016, we have received clearance from the U.S. Food and Drug Administration, or the FDA, for three investigational new drug applications, or INDs, and successfully advanced these three programs into clinical development. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development beginning in 2021.

By focusing on developing agents using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of six distinct programs spanning methyltransferases, kinases, protein-protein interactions and targeted protein degraders. Our pipeline is geared towards serving patients with high unmet medical need where there are limited or no treatment options. We are exploring therapies in both solid tumors and hematological malignancies such as adenoid cystic carcinoma, or ACC, homologous recombination deficient positive, or HRD+, cancers, myelofibrosis, or MF, and glioblastoma multiforme, or GBM, amongst others. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

Our lead product candidates are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. The potency and selectivity of our product candidates is supported by preclinical data demonstrating nanomolar inhibition of PRMT5 and no inhibition of related enzymes at 1,000 times higher concentration of our product candidates. We are currently advancing our first clinical candidate, PRT543, in a Phase 1 clinical trial in select solid tumors and myeloid malignancies in patients who are refractory to or intolerant of established therapies. Interim Phase 1 results indicate dose-dependent increases in exposure and target engagement, and we have observed early signs of clinical activity, including an ongoing confirmed complete response, or CR, in a patient with HRD+ high grade serous ovarian cancer through nine months of therapy. A complete response is defined as the disappearance of all target lesions. We will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by the FDA or other regulatory authorities, and while such approval is not guaranteed, we are encouraged by the clinical activity as of the date of this prospectus. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

We are also advancing PRT811, a second PRMT5 inhibitor that we have optimized for high brain exposure, in a Phase 1 clinical trial in solid tumors, including GBM. As of the date of this prospectus, the trial has

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demonstrated early signs of clinical activity and tolerability. The previously disclosed refractory GBM patient whose tumor had demonstrated a 66% reduction on monotherapy PRT811 subsequently underwent a follow-up MRI at week 18 and the regression has improved to 77% from baseline, confirming a partial response, or PR, per RANO (response assessment in neuro-oncology) criteria. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the first half of 2021 and anticipate obtaining initial clinical data from these expansion cohorts by the end of 2021.

PRT1419, our third clinical candidate, is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. The potency and selectivity of PRT1419 is supported by preclinical data demonstrating nanomolar inhibition of MCL1 and no inhibition of related enzymes at 200 times higher concentration of our product candidate. We have begun enrolling patients with hematologic malignancies, including patients with myelodysplastic syndrome, or MDS, acute myeloid leukemia, or AML, non-Hodgkin's lymphoma, or NHL, and multiple myeloma, or MM, into the Phase 1 clinical trial for PRT1419. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the second half of 2021.

We were incorporated in February 2016 under the laws of the State of Delaware. Since inception, we have devoted substantially all of our resources to developing product and technology rights, conducting research and development, organizing and staffing our company, business planning and raising capital. We have incurred recurring losses, the majority of which are attributable to research and development activities, and negative cash flows from operations. We have funded our operations primarily through the sale of convertible preferred stock and common stock through our IPO. Our net loss was \$14.7 million and \$27.6 million for the years ended December 31, 2018 and 2019, respectively, and \$16.8 and \$37.7 million for the three and nine months ended September 30, 2020. As of September 30, 2020, we had an accumulated deficit of \$88.2 million. Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures, and to a lesser extent, general and administrative expenditures. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of one or more of our current or future product candidates. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we advance our product candidates through all stages of development and clinical trials and, ultimately, seek regulatory approval. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical trials and our expenditures on other research and development activities.

We will need to raise substantial additional capital to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we plan to finance our operations through the sale of equity, debt financings or other capital sources, which may include collaborations with other companies or other strategic transactions. There are no assurances that we will be successful in obtaining an adequate level of financing as and when needed to finance our operations on terms acceptable to us or at all. Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. If we are unable to secure adequate additional funding, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more product candidates or delay our pursuit of potential in-licenses or acquisitions.

As of September 30, 2020, we had \$234.8 million in cash and cash equivalents. We expect our existing cash and cash equivalents, together with the anticipated net proceeds from this offering, to enable us to fund our operating expenses and capital expenditure requirements into .

COVID-19 Impact

We are continuing to proactively monitor and assess the current coronavirus disease 2019, or COVID-19, global pandemic. Since early March we have been monitoring the potential impact on our business

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that may result from this rapidly evolving crisis and to avoid any unnecessary potential delays to our programs. At this time, our lead programs and research activities remain on track. The safety and well-being of employees, patients and partners is our highest priority.

Components of Results of Operations

Revenue

To date, we have not recognized any revenue from any sources, including from product sales, and we do not expect to generate any revenue from the sale of products in the foreseeable future. If our development efforts for our product candidates are successful and result in regulatory approval, or license agreements with third parties, we may generate revenue in the future from product sales. However, there can be no assurance as to when we will generate such revenue, if at all.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred in connection with the discovery and development of our product candidates. We expense research and development costs as incurred, including:

- expenses incurred to conduct the necessary discovery-stage laboratory work, preclinical studies and clinical trials required to obtain regulatory approval;
- personnel expenses, including salaries, benefits and stock-based compensation expense for our employees engaged in research and development functions;
- costs of funding research performed by third parties, including pursuant to agreements with clinical research organizations, or CROs, that conduct our clinical trials, as well as investigative sites, consultants and CROs that conduct our preclinical and nonclinical studies;
- expenses incurred under agreements with contract manufacturing organizations, or CMOs, including manufacturing scale-up expenses and the cost of acquiring and manufacturing preclinical study and clinical trial materials;
- fees paid to consultants who assist with research and development activities;
- expenses related to regulatory activities, including filing fees paid to regulatory agencies; and
- allocated expenses for facility costs, including rent, utilities, depreciation and maintenance.

We track outsourced development costs and other external research and development costs to specific product candidates on a program-by-program basis, fees paid to CROs, CMOs and research laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. However, we do not track our internal research and development expenses on a program-by-program basis as they primarily relate to compensation, early research and other costs which are deployed across multiple projects under development.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect our research and development expenses to increase significantly over the next several years as we increase personnel costs, including stock-based compensation, conduct our clinical trials, including later-stage clinical trials, for current and future product candidates and prepare regulatory filings for our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel expenses, including salaries, benefits and stock-based compensation expense, for employees and consultants in executive, finance and accounting,

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legal, operations support, information technology and human resource functions. General and administrative expense also includes corporate facility costs not otherwise included in research and development expense, including rent, utilities, depreciation and maintenance, as well as legal fees related to intellectual property and corporate matters and fees for accounting and consulting services.

We expect that our general and administrative expense will increase in the future to support our continued research and development activities, potential commercialization efforts and increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, legal support and accountants, among other expenses. Additionally, we have seen, and may continue to see, increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with the requirements of Nasdaq and the Securities and Exchange Commission, or SEC, insurance and investor relations costs. If any of our current or future product candidates obtains U.S. regulatory approval, we expect that we would incur significantly increased expenses associated with building a sales and marketing team.

Other Income, Net

Other income, net consists primarily of interest earned on our cash equivalents and grant income received from the State of Delaware. We anticipate re-applying for the grant from the State of Delaware from time to time as long as we maintain qualifying headcount levels in the State of Delaware. We expect our interest income, net to increase due to our investment of cash received from the IPO.

Income Taxes

Since our inception, we have not recorded any income tax benefits for the net operating losses, or NOLs, we have incurred or for our research and development tax credits, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our NOLs and tax credits will not be realized.

Results of Operations

Comparison of the Three Months Ended September 30, 2019 and 2020

The following table sets forth our results of operations for the three months ended September 30, 2019 and 2020.

(in thousands)	Three months ended September 30,		Change
	2019	2020	
Operating expenses:			
Research and development	\$ 5,490	\$ 15,293	\$ 9,803
General and administrative	1,394	2,851	1,457
Total operating expenses	6,884	18,144	11,260
Loss from operations	(6,884)	(18,144)	(11,260)
Other income, net	150	1,384	1,234
Net loss	<u>\$(6,734)</u>	<u>\$(16,760)</u>	<u>\$(10,026)</u>

Research and Development Expenses

Research and development expenses increased by \$9.8 million from \$5.5 million for the three months ended September 30, 2019 to \$15.3 million for the three months ended September 30, 2020. The increase was mainly due to increased clinical research costs for the PRT543 and PRT811 clinical trials and increased costs associated

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with the initiation of the clinical trial for PRT1419, which began in the third quarter of 2020. We also incurred an increase in chemistry, manufacturing and other costs for those trials. We track our external research and development expenses on a program-by-program basis, such as fees paid to CROs, CMOs and research laboratories in connection with our pre-clinical development, process development, manufacturing and clinical development activities. However, we do not track our internal research and development expenses on a program-by-program basis as they primarily relate to compensation, early research and other costs which are deployed across multiple projects under development.

Research and development expenses by program are summarized in the table below:

(in thousands)	Three months ended September 30,	
	2019	2020
PRT543	\$ 971	\$ 4,354
PRT811	302	1,899
PRT1419	934	2,533
Discovery programs	1,609	2,823
Internal costs, including personnel related	1,674	3,684
	<u>\$5,490</u>	<u>\$ 15,293</u>

General and Administrative Expenses

General and administrative expenses increased by \$1.5 million from \$1.4 million for the three months ended September 30, 2019 to \$2.9 million for the three months ended September 30, 2020. The increase was primarily due to an increase in personnel related expense due to increases in employee headcount and an increase in our professional fees as we expanded our operations to support our research and development efforts and incurred additional costs to operate as a public company.

Other Income, net

Other income, net increased by \$1.2 million primarily due to the receipt and recognition of a research and development tax credit from the State of Delaware in the third quarter of 2020.

Comparison of the Nine Months Ended September 30, 2019 and 2020

The following table sets forth our results of operations for the nine months ended September 30, 2019 and 2020.

(in thousands)	Nine months ended September 30,		Change
	2019	2020	
Operating expenses:			
Research and development	\$ 15,430	\$ 33,605	\$ 18,175
General and administrative	2,584	5,712	3,128
Total operating expenses	<u>18,014</u>	<u>39,317</u>	<u>21,303</u>
Loss from operations	(18,014)	(39,317)	(21,303)
Other income, net	483	1,638	1,155
Net loss	<u>\$ (17,531)</u>	<u>\$ (37,679)</u>	<u>\$ (20,148)</u>

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Research and Development Expenses

Research and development expenses increased by \$18.2 million from \$15.4 million for the nine months ended September 30, 2019 to \$33.6 million for the nine months ended September 30, 2020. The increase was mainly due to increased patient enrollment and monitoring costs for the PRT543 and PRT811 clinical trials and increased costs associated with the initiation of the clinical trial for PRT1419, which began in the third quarter of 2020. We also incurred an increase in chemistry, manufacturing and other costs for those trials. We track our external research and development expenses on a program-by-program basis, such as fees paid to CROs, CMOs and research laboratories in connection with our pre-clinical development, process development, manufacturing and clinical development activities. However, we do not track our internal research and development expenses on a program-by-program basis as they primarily relate to compensation, early research and other costs which are deployed across multiple projects under development.

Research and development expenses by program are summarized in the table below:

(in thousands)	Nine months ended September 30,	
	2019	2020
PRT543	\$ 3,642	\$ 8,414
PRT811	2,202	3,465
PRT1419	1,119	6,540
Discovery programs	3,662	4,793
Internal costs, including personnel related	4,805	10,393
	<u>\$ 15,430</u>	<u>\$ 33,605</u>

General and Administrative Expenses

General and administrative expenses increased by \$3.1 million from \$2.6 million for the nine months ended September 30, 2019 to \$5.7 million for the nine months ended September 30, 2020. The increase was primarily due to an increase in personnel related expense due to increases in employee headcount and an increase in our professional fees as we expanded our operations to support our research and development efforts. We also incurred additional expenses as we began to operate as a public company.

Other Income, net

Other income, net increased by \$1.2 million primarily due to the receipt and recognition of a research and development tax credit from the State of Delaware in the third quarter of 2020.

Comparison of the Years Ended December 31, 2018 and 2019

The following table sets forth our results of operations for the years ended December 31, 2018 and 2019.

(in thousands)	Year ended December 31,		Change
	2018	2019	
Operating expenses:			
Research and development	\$ 12,621	\$ 24,279	\$ 11,658
General and administrative	2,354	3,830	1,476
Total operating expenses	<u>14,975</u>	<u>28,109</u>	<u>13,134</u>
Loss from operations	(14,975)	(28,109)	(13,134)
Other income, net	295	539	244
Net loss	<u>\$(14,680)</u>	<u>\$(27,570)</u>	<u>\$(12,890)</u>

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Research and Development Expenses

Research and development expenses increased by \$11.7 million from \$12.6 million for the year ended December 31, 2018 to \$24.3 million for the year ended December 31, 2019. The increase was mainly due to commencing clinical trials for PRT543 and PRT811 in late 2018 and during 2019, respectively, and the associated ramp up of chemistry, manufacturing and other costs for those trials.

Research and development expenses by program are summarized in the table below:

(in thousands)	Year ended December 31,	
	2018	2019
PRT543	\$ 3,870	\$ 5,742
PRT811	2,759	3,150
PRT1419	—	2,925
Discovery programs	2,409	5,323
Internal costs, including personnel related	3,583	7,139
	<u>\$ 12,621</u>	<u>\$ 24,279</u>

General and Administrative Expenses

General and administrative expenses increased by \$1.5 million from \$2.4 million for the year ended December 31, 2018 to \$3.8 million for the year ended December 31, 2019. The increase was primarily due to an increase in personnel related expense due to increases in employee headcount and an increase in our professional fees as we expanded our operations to support our research and development efforts.

Other Income, net

Other income, net increased by \$0.2 million from \$0.3 million for the year ended December 31, 2018 to \$0.5 million for the year ended December 31, 2019, primarily due to additional interest earned on the investment of our cash proceeds balances.

Liquidity and Capital Resources

Overview

Since our inception, we have not recognized any revenue and have incurred operating losses and negative cash flows from our operations. We have not yet commercialized any product and we do not expect to generate revenue from sales of any products for several years, if at all. Since our inception through August 2020, we have funded our operations through the sale of convertible preferred stock, receiving aggregate net proceeds of \$144.4 million. Upon the completion of our IPO in September 2020, we received net proceeds of \$166.6 million. As of September 30, 2020, we had \$234.8 million in cash and cash equivalents and had an accumulated deficit of \$88.2 million. We expect our existing cash and cash equivalents, together with the anticipated net proceeds from this offering, to enable us to fund our operating expenses and capital expenditure requirements into . We have based these estimates on assumptions that may prove to be imprecise, and we could utilize our available capital resources sooner than we expect.

Funding Requirements

Our primary use of cash is to fund operating expenses, primarily research and development expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable, accrued expenses and prepaid expenses.

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Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

- the scope, timing, progress and results of discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs of manufacturing our product candidates for clinical trials and in preparation for marketing approval and commercialization;
- the extent to which we enter into collaborations or other arrangements with additional third parties in order to further develop our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs and fees associated with the discovery, acquisition or in-license of additional product candidates or technologies;
- expenses needed to attract and retain skilled personnel;
- costs associated with being a public company;
- the costs required to scale up our clinical, regulatory and manufacturing capabilities;
- the costs of future commercialization activities, if any, including establishing sales, marketing, manufacturing and distribution capabilities, for any of our product candidates for which we receive marketing approval; and
- revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval.

We will need additional funds to meet operational needs and capital requirements for clinical trials, other research and development expenditures, and business development activities. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

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Cash Flows

The following table shows a summary of our cash flows for the periods indicated:

(in thousands)	Year ended December 31,		Nine months ended September 30,	
	2018	2019	2019	2020
Cash used in operating activities	\$(12,954)	\$(25,665)	\$(17,196)	\$(31,330)
Cash used in investing activities	(529)	(780)	(581)	(292)
Cash provided by financing activities	17,937	29,729	29,822	247,535
Net increase in cash and cash equivalents	<u>\$ 4,454</u>	<u>\$ 3,284</u>	<u>\$ 12,045</u>	<u>\$215,913</u>

Operating Activities

During the year ended December 31, 2018, we used \$13.0 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$14.7 million, offset by a \$1.4 million net decrease in our operating assets and liabilities and noncash charges of \$0.3 million, which consisted of \$0.1 million in depreciation and amortization and \$0.2 million in stock-based compensation. The primary use of cash was to fund our operations related to the development of our product candidates.

During the year ended December 31, 2019, we used \$25.7 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$27.6 million, offset by a \$0.7 million net decrease in our operating assets and liabilities and noncash charges of \$1.2 million, which consisted of \$0.4 million in depreciation and \$0.8 million in stock-based compensation. The primary use of cash was to fund our operations related to the development of our product candidates.

During the nine months ended September 30, 2019, we used \$17.2 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$17.5 million and a net increase of \$0.4 million in our operating assets and liabilities, offset by \$0.8 million of noncash charges, which consisted of \$0.3 million in depreciation and amortization and \$0.5 million in stock-based compensation. The primary use of cash was to fund our operations related to the development of our product candidates.

During the nine months ended September 30, 2020, we used \$31.3 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$37.7 million, offset by a \$3.5 million net decrease in our operating assets and liabilities and noncash charges of \$2.9 million, which consisted of \$0.4 million in depreciation and \$2.5 million in stock-based compensation. The primary use of cash was to fund our operations related to the development of our product candidates.

Investing Activities

During the years ended December 31, 2018 and 2019, we used \$0.5 million and \$0.8 million of cash, respectively, for the purchase of property and equipment.

During the nine months ended September 30, 2019 and 2020, we used \$0.6 million and \$0.3 million of cash, respectively, for the purchase of property and equipment.

Financing Activities

During the year ended December 31, 2018, financing activities provided \$17.9 million from the sale of our Series A convertible preferred stock. During the year ended December 31, 2019, financing activities provided \$29.7 million of cash. Net cash provided by financing activities for the year ended December 31, 2019 consisted of \$29.8 million from the sale of our Series B convertible preferred stock, offset by payments of \$0.1 million for our capital lease obligation.

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During the nine months ended September 30, 2019 net cash provided by financing activities consisted of \$29.8 million from the sale of our Series B convertible preferred stock and \$5,000 of proceeds received from the exercise of stock options, offset by payments of \$31,000 for our capital lease obligation. During the nine months ended September 30, 2020, financing activities provided \$247.5 million. During the nine months ended September 30, 2020, we completed our IPO and received net cash of \$167.9 million. We also received \$49.8 million from the sale of our Series C convertible preferred stock, \$29.9 million from the sale of our Series B convertible preferred stock and \$96,000 from the exercise of stock options. During the nine months ended September 30, 2020, we made \$0.3 million in payments for our capital lease obligation.

Contractual Obligations and Other Commitments

The following table summarizes our contractual obligations and commitments at December 31, 2019:

(in thousands)	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years	Total
Operating leases ⁽¹⁾	\$ 973	\$ 21	\$ —	\$ —	\$ 994
Capital lease, including interest	281	—	—	—	281
Total	\$ 1,254	\$ 21	\$ —	\$ —	\$1,275

(1) In November 2020, we extended the lease that was set to expire in December 2021 until December 2022.

The commitment amounts in the table above are associated with contracts that are enforceable and legally binding and that specify all significant terms, including fixed or minimum services to be used, fixed, minimum or variable price provisions, and the approximate timing of the actions under the contracts. Payments due upon cancellation consisting only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation are not included in the preceding table as the amount and timing of such payments are not known.

Off-Balance Sheet Arrangements

During the periods presented, we did not have, nor do we currently have, any relationships with unconsolidated entities or financial partnerships, including entities sometimes referred to as structured finance or special purpose entities that were established for the purpose of facilitating off-balance sheet arrangements or other contractually narrow or limited purposes. We do not engage in off-balance sheet financing arrangements. In addition, we do not engage in trading activities involving non-exchange traded contracts. We therefore believe that we are not materially exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in these relationships.

Critical Accounting Policies

This management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 3 to our audited financial statements included elsewhere in this prospectus, we believe the following accounting policy is the most critical to the judgments and estimates used in the preparation of our financial statements.

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Research and Development Expenses

Research and development expenses consist primarily of costs incurred in connection with the development of our product candidates. We expense research and development costs as incurred.

We accrue an expense for preclinical studies and clinical trial activities performed by our vendors based upon estimates of the proportion of work completed. We determine the estimates by reviewing contracts, vendor agreements and purchase orders, and through discussions with our internal clinical personnel and external service providers as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services. However, actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan.

We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known at that time. If the actual timing of the performance of services or the level of effort varies from the estimate, we will adjust the accrual accordingly. Nonrefundable advance payments for goods and services, including fees for clinical trial expenses, process development or manufacturing and distribution of clinical supplies that will be used in future research and development activities, are deferred and recognized as expense in the period that the related goods are consumed or services are performed.

Stock-Based Compensation

We measure compensation expense for all stock-based awards based on the estimated fair value of the stock-based awards on the grant date. We use the Black-Scholes option pricing model to value our stock option awards. We recognize compensation expense on a straight-line basis over the requisite service period, which is generally the vesting period of the award. We have not issued awards for which vesting is subject to a market or performance conditions.

The Black-Scholes option-pricing model requires the use of subjective assumptions that include the expected stock price volatility and the fair value of the underlying common stock on the date of grant. See Note 9 to our audited financial statements and Note 7 to our unaudited interim financial statements included elsewhere in this prospectus for information concerning certain of the specific assumptions we used in applying the Black-Scholes option pricing model to determine the estimated fair value of our stock options granted.

Because our common stock was not previously publicly traded, the fair value of the common stock underlying our stock options was determined on each grant date by our board of directors, with input from management, considering our most recently available third-party valuation of common shares.

The third-party valuations of our common stock were performed using methodologies, approaches and assumptions consistent with the American Institute of Certified Public Accountants, *Audit and Accounting Practice Aid Series: Valuation of Privately Held Company Equity Securities Issued as Compensation*. In addition, our board of directors considered various objective and subjective factors to estimate the estimated fair value of our common stock, including:

- the prices of our preferred stock sold to outside investors in arm's length transactions, and the rights, preferences and privileges of our preferred stock as compared to those of our common stock, including the liquidation preferences of our preferred stock;
- the estimated value of each security both outstanding and anticipated;
- the anticipated capital structure, which will directly impact the value of the currently outstanding securities;
- our results of operations and financial position;
- the status of our research and development efforts;

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- the composition of, and changes to, our management team and board of directors;
- the lack of liquidity of our common stock as a private company;
- our stage of development and business strategy and the material risks related to our business and industry;
- external market conditions affecting the life sciences and biotechnology industry sectors;
- U.S. and global economic conditions;
- the likelihood of achieving a liquidity event for the holders of our common stock, such as an initial public offering, or IPO, or a sale of our company, given prevailing market conditions; and
- the market value and volatility of comparable companies.

In determining the estimated fair value of common stock, our board of directors considered the subjective factors discussed above in conjunction with the most recent valuations of our common stock that were prepared by an independent third party.

Following the closing of our IPO, the fair value of our common stock is the closing price of our common stock on the Nasdaq Global Select Market as reported on the date of the grant.

JOBS Act Accounting Election

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies.

We have elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest of (1) the last day of our first fiscal year (a) in which we have total annual gross revenues of at least \$1.07 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30th, (2) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period and (3) December 31, 2025.

Recent Accounting Pronouncements

See Note 3 to our audited financial statements included elsewhere in this prospectus for a description of recent accounting pronouncements applicable to our financial statements.

Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risk related to changes in interest rates. As of September 30, 2020, we had cash and cash equivalents of \$234.8 million consisting of bank deposits and a commercial money market account. Due to the short-term duration of our cash equivalents, an immediate 10% change in interest rates would not have a material effect on the fair market value.

Emerging Growth Company and Smaller Reporting Company Status

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an “emerging growth company” can take advantage of the extended transition

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period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from complying with new or revised accounting standards and, therefore, will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements under the JOBS Act, including without limitation, exemption to the requirements for providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act. We will remain an emerging growth company until the earlier to occur of (a) the last day of the fiscal year (i) following the fifth anniversary of the completion of our IPO, (ii) in which we have total annual gross revenues of at least \$1.07 billion or (iii) in which we are deemed to be a "large accelerated filer" under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30th, or (b) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than \$700.0 million and our annual revenue is less than \$100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company after if either (i) the market value of our stock held by non-affiliates is less than \$250.0 million or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than \$700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

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BUSINESS

Overview

We are a clinical-stage precision oncology company focused on discovering and developing small molecule therapies optimized to target the key driver mechanisms in cancers with high unmet need. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our target class- and technology platform-agnostic approach, we have built an efficient, fully-integrated drug discovery engine to identify compelling biological targets and create new chemical entities, or NCEs, that we rapidly advance into clinical development. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our rapid progress in creating a wholly-owned, internally developed pipeline. Since our inception in 2016, we have received clearance from the U.S. Food and Drug Administration, or the FDA, for three investigational new drug applications, or INDs, and successfully advanced these three programs into clinical development. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development beginning in 2021.

By focusing on developing agents using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of six distinct programs spanning methyltransferases, kinases, protein-protein interactions and targeted protein degraders. Our pipeline is geared towards serving patients with high unmet medical need where there are limited or no treatment options. We are exploring therapies in both solid tumors and hematological malignancies such as adenoid cystic carcinoma, or ACC, homologous recombination deficient positive, or HRD+, cancers, myelofibrosis, or MF, and glioblastoma multiforme, or GBM, amongst others. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

Our lead product candidates are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. The potency and selectivity of our product candidates is supported by preclinical data demonstrating nanomolar inhibition of PRMT5 and no inhibition of related enzymes at 1,000 times higher concentration of our product candidates. We are currently advancing our first clinical candidate, PRT543, in a Phase 1 clinical trial in select solid tumors and myeloid malignancies in patients who are refractory to or intolerant of established therapies. Interim Phase 1 results indicate dose-dependent increases in exposure and target engagement, and we have observed early signs of clinical activity, including an ongoing confirmed complete response, or CR, in a patient with HRD+ high grade serous ovarian cancer through nine months of therapy. A complete response is defined as the disappearance of all target lesions. While we will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by the FDA or other regulatory authorities, and while such approval is not guaranteed, we are encouraged by the clinical activity as of the date of this prospectus. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

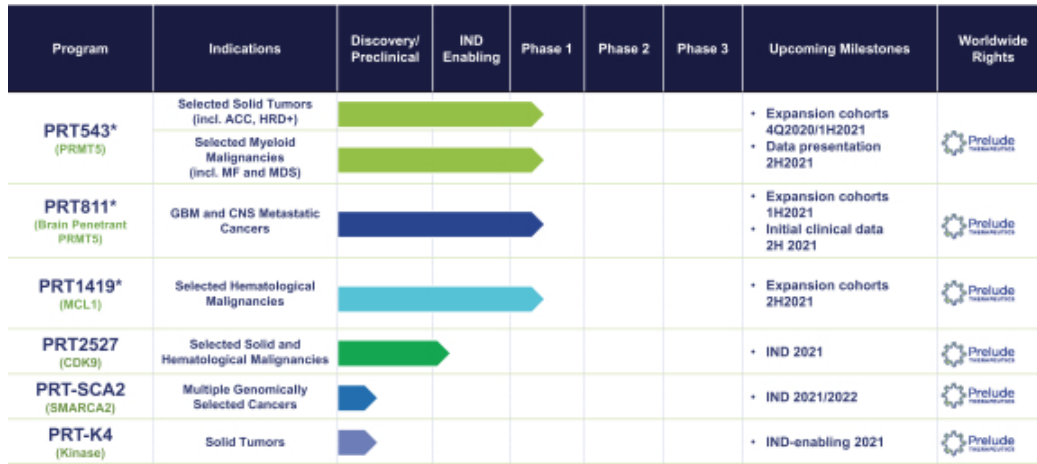
We are also advancing PRT811, a second PRMT5 inhibitor that we have optimized for high brain exposure, in a Phase 1 clinical trial in solid tumors, including GBM. As of the date of this prospectus, the trial has demonstrated early signs of clinical activity and tolerability. The previously disclosed refractory GBM patient whose tumor had demonstrated a 66% reduction on monotherapy PRT811 subsequently underwent a follow-up MRI at week 18 and the regression has improved to 77% from baseline, confirming a partial response, or PR, per RANO (response assessment in neuro-oncology) criteria. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the first half of 2021 and anticipate obtaining initial clinical data from these expansion cohorts by the end of 2021.

PRT1419, our third clinical candidate, is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. The potency and selectivity of PRT1419 is supported by preclinical data demonstrating

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nanomolar inhibition of MCL1 and no inhibition of related enzymes at 200 times higher concentration of our product candidate. We have begun enrolling patients with hematologic malignancies, including patients with myelodysplastic syndrome, or MDS, acute myeloid leukemia, or AML, non-Hodgkin’s lymphoma, or NHL, and multiple myeloma, or MM, into the Phase 1 clinical trial for PRT1419. We expect to begin enrolling patients in the expansion portion of the Phase 1 clinical trial in the second half of 2021.

Our pipeline is summarized in the figure below:



* Currently in Phase 1 dose escalation

Prelude Discovery and Development Approach

We carefully evaluate and select our targets based on three key pillars, which provide a framework for optimizing our drug discovery and development efforts.

- Identify target mechanisms with compelling biological rationale
 - *Current target mechanisms of focus include: transcriptional regulation, deoxyribonucleic acid, or DNA, repair pathway, cell cycle regulation, exploitation of synthetic lethality and brain penetrant molecules*
- Leverage our advanced medicinal chemistry capabilities to create better product candidates
 - *We view all target classes equally and strive to invent clinical candidates that meet our desired target product profiles*
- Pursue targets that drive cancers with high unmet need
 - *Focus on targets that allow us to select patients and cancers with high unmet need with no approved therapies, or patient populations that are underserved by approved treatments*

Once we have identified optimal targets using the three pillars above, we engage our unique discovery engine to rapidly and efficiently invent and develop molecules. We believe our expertise, capabilities and experience to select high value biological targets and invent molecules with an optimized balance of biological and chemical properties differentiates us from others in the precision oncology space. We believe our unique discovery engine will enable us to continue delivering a new IND every 12 to 18 months.

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We design our clinical trials to leverage the broad utility of our compounds with a focus on efficient regulatory pathways to enable our potentially transformative medicines to quickly reach patients with high unmet medical need. By focusing on validated cancer signaling pathways and early clinical proof-of-concept, we seek to advance our programs through expedited approval processes.

Our Product Candidates

Our first two candidates, PRT543 and PRT811, are designed to be potent, selective and oral inhibitors of PRMT5. We believe targeting PRMT5 has broad applicability and a strong scientific rationale for the treatment of cancer as it regulates transcription, translation and messenger ribonucleic acid, or mRNA, as well as the splicing of cancer related genes. Inhibition of PRMT5 has been observed to suppress tumor growth and produce synthetic lethality preclinically.

PRT543, our first clinical candidate, is currently in a Phase 1 clinical trial in advanced solid tumors and select myeloid malignancies. We have been encouraged by both the clinical activity and tolerability data that have been seen in 61 patients (42 with advanced solid tumors, one with NHL, 11 with MF and seven with MDS) that have enrolled into the study as of December 16, 2020. We have observed early signs of clinical activity, including a durable confirmed CR per RECIST v1.1, in a patient with HRD+ high grade serous ovarian cancer, in the 35 mg 5x/week (once a day, for five days, with two days off) cohort. This patient has received 9 months of study therapy as of December 16, 2020 and remains in CR. We will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by FDA or other regulatory authorities, and such approval is not guaranteed. In addition, extended duration of therapy and improvements in symptoms have been observed in several patients with MF, with one patient demonstrating a response of clinical improvement and another patient showing an approximately 66% reduction in Total Symptom Score, or TSS, a validated clinical endpoint in MF. Clinical improvement means an achievement in anemia, spleen, or symptom response without progressive disease or increase in the severity of anemia, thrombocytopenia or neutropenia. We have begun enrolling patients into the expansion portion of the Phase 1 clinical trial in select tumor types that are potentially driven by PRMT5 dysregulation. These tumor types include ACC, MF, genomically selected MDS and HRD+ tumors. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

PRT811, our second clinical candidate, is currently advancing in the dose escalation portion of a Phase 1 clinical trial in solid tumors, including GBM and primary central nervous system lymphomas, or PCNSL. PRT811 has been optimized for high brain exposure and hence we believe is uniquely positioned to treat PRMT5 sensitive CNS cancers. We have been encouraged by both the clinical activity and tolerability data that have been seen in 24 patients (eight with GBM, 16 with various advanced solid tumors) that have enrolled into the dose escalation portion of the study as of December 16, 2020. We have observed early signs of clinical activity in a refractory GBM patient whose tumor initially demonstrated a 66% reduction on monotherapy PRT811 at week 6, and subsequently underwent a follow-up MRI at week 18, and the regression has improved to 77% from baseline, confirming a PR per RANO (response assessment in neuro-oncology) criteria. This patient has received 5 months of study therapy as of December 16, 2020 and remains in PR and is clinically stable. We will need to enroll and demonstrate objective responses in additional patients to support further development and potential approval by FDA or other regulatory authorities, and such approval is not guaranteed. We plan to initially enroll patients in the expansion portion of the clinical trial with GBM, PCNSL and solid tumors with metastatic disease to the CNS once we have established an expansion dose. We expect these expansions to begin in the first half of 2021 and anticipate initial clinical results from these expansion cohorts by the end of 2021.

PRT1419, our third clinical candidate, is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. We believe hematological malignancies are particularly sensitive to MCL1 inhibitors. MCL1 upregulation has been noted as a mechanism of acquired resistance to venetoclax and tyrosine kinase inhibitors,

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or TKIs. In addition, certain solid tumors are responsive to MCL1 inhibition, informing a potential patient selection strategy. We have enrolled four patients into the Phase 1 clinical trial investigating oral PRT1419 in high risk MDS, AML, NHL and MM. Additionally, during the fourth quarter of 2020 we filed an IND with the FDA for an intravenous, or IV, formulation of PRT1419, which we plan to evaluate in various advanced solid tumors. We believe that the physicochemical and pharmacological properties of PRT1419 allow the optionality of administering PRT1419 by either oral or IV routes.

In addition to our three clinical stage candidates, our two most advanced preclinical programs target cyclin-dependent kinase 9, or CDK9, and Brahma homologue, or BRM, otherwise known as SMARCA2, respectively. PRT2527 designed to be a potent and selective CDK9 inhibitor, has entered IND-enabling studies with an IND submission expected in 2021. We have also identified SMARCA2 protein degraders that appear to be potent based on preclinical data demonstrating degradation of SMARCA2 at sub-nanomolar concentration. Optimization of the lead compound, PRT-SCA2, is progressing, and we expect to initiate IND-enabling studies in 2021. Our sixth program is exploring a kinase target for solid tumors. We are optimizing our lead compound, PRT-K4, and expect to begin IND-enabling studies in 2021.

Our Team

We were founded in 2016 by Kris Vaddi, Ph.D., a founding scientist at Incyte, and have assembled an experienced management team and board of directors with deep expertise in oncology and drug development. We have built from the “ground up” our internal discovery team, led by scientific and medical teams with deep expertise and proven capabilities in inventing and rapidly advancing small molecule medicines that address important gaps in the current precision oncology ecosystem. Members of our management team have successfully developed and commercialized numerous drugs such as Jakafi, Olumiant, Velcade, VITRAKVI, Retevmo, Taltrex and Pemazyre.

Our Strategy

We aim to create better targeted and more effective cancer therapies. Our goal is to transform the lives of patients with cancer by leveraging the core competencies of our experienced team in medicinal chemistry, cancer biology and clinical development to bring novel drugs to market. We intend to become a fully integrated patient-focused precision oncology company by pursuing the following objectives:

- **Rapidly progress our lead product candidates, PRT543 and PRT811, through clinical development in patients with select solid tumors and hematological malignancies.** Our oral PRMT5 inhibitor candidates target multiple indications, with an initial focus on ACC, HRD+ tumors, myeloid and CNS malignancies, and have the potential for accelerated approval. We are currently advancing our first clinical candidate, PRT543, in a Phase 1 clinical trial in select solid tumors and myeloid malignancies. Interim Phase 1 results indicate dose-dependent increases in exposure and target engagement, and we have observed early signs of clinical activity, including an ongoing durable confirmed CR in a highly-refractory HRD+ ovarian cancer patient and prolonged stable disease, or SD, defined as failure to meet the definitions of either objective clinical response or progressive disease, in multiple patients with myeloid malignancies. We are also advancing PRT811, a second PRMT5 inhibitor that we have optimized for high brain exposure, in a Phase 1 clinical trial in solid tumors, including GBM. The previously disclosed refractory GBM patient whose tumor had demonstrated a 66% reduction on monotherapy PRT811 has subsequently undergone a follow-up MRI at week 18 and the regression has improved to 77% from baseline, confirming a PR per RANO (response assessment in neuro-oncology) criteria. We began patient enrollment into the solid tumor expansion portion of the PRT543 Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. Patient enrollment into the expansion cohort for PRT811 is expected to begin in the first half of 2021 as well. We anticipate presenting initial clinical results for PRT543 in the second half of 2021 and obtaining initial clinical results for PRT811 by the end of 2021.

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- **Expediently advance PRT1419, our MCL1 inhibitor, through clinical development in patients with select hematological malignancies.** MCL1 is an oncogenic driver and a major resistance mechanism to B-cell lymphoma 2, or BCL2, inhibitors. We have enrolled four patients into a Phase 1 clinical trial investigating oral PRT1419 in high risk MDS, AML, NHL and MM patients. Additionally, during the fourth quarter of 2020, we filed an IND for an IV formulation of PRT1419, which we plan to evaluate in various advanced solid tumors, giving us the optionality of both oral and IV routes of administration.
- **Continue to advance our earlier stage programs, including a CDK9 inhibitor and a SMARCA2 degrader.** PRT2527, designed to be a potent and selective CDK9 inhibitor, has entered IND-enabling studies with an IND submission expected in 2021. We have also identified potent SMARCA2 protein degraders based on data demonstrating degradation of SMARCA2 at sub-nanomolar concentration. Optimization of the lead compound, PRT-SCA2, is progressing and we expect to initiate IND-enabling studies in 2021.
- **Leverage our cancer biology and medicinal chemistry expertise to consistently deliver one new IND every 12 – 18 months.** We are committed to developing drugs that take a unique approach to precision oncology by focusing on broad mechanisms that have multiple links to oncogenic driver pathways in select patients. Utilizing our unique fully-integrated targeted oncology discovery engine, we will continue to pursue small-molecule therapies optimized to effectively target the key driver mechanisms in cancers with high unmet need, regardless of target class or technology platform. Since our inception in 2016, we have received FDA clearance for three INDs and successfully advanced these three programs into clinical development. We aim to continue to deliver on our goal of creating better targeted and more effective cancer therapies for patients with high unmet need.
- **Opportunistically evaluate strategies to accelerate development timelines and maximize the value of our product candidate pipeline.** We have developed each of our product candidates based on our internal capabilities, and we currently have worldwide development and commercial rights to each of our candidates. Given our ability to efficiently invent target class agnostic, small molecule agents that have broad applicability, including potential indications beyond oncology, we may choose to opportunistically enter into strategic collaborations that enable us to broaden our clinical or commercial impact.

Our Pipeline

Consistent with our target class agnostic approach, our current pipeline includes six distinct programs spanning methyltransferases, kinases, protein-protein interactions and targeted protein degraders. Since our inception in 2016, we have received clearance for three INDs and advanced these three programs into clinical development for multiple solid tumors and hematological malignancies. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development

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beginning in 2021. We have structured and resourced our research and development, or R&D, organization with the goal and expectation of continuing to deliver a new IND every 12 to 18 months.

Program	Indications	Discovery/ Preclinical	IND Enabling	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Worldwide Rights
PRT543* (PRMT5)	Selected Solid Tumors (incl. ACC, HRD+)						<ul style="list-style-type: none"> Expansion cohorts 4Q2020/1H2021 Data presentation 2H2021 	
	Selected Myeloid Malignancies (incl. MF and MDS)							
PRT811* (Brain Penetrant PRMT5)	GBM and CNS Metastatic Cancers						<ul style="list-style-type: none"> Expansion cohorts 1H2021 Initial clinical data 2H 2021 	
PRT1419* (MCL1)	Selected Hematological Malignancies						<ul style="list-style-type: none"> Expansion cohorts 2H2021 	
PRT2527 (CDK9)	Selected Solid and Hematological Malignancies						<ul style="list-style-type: none"> IND 2021 	
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers						<ul style="list-style-type: none"> IND 2021/2022 	
PRT-K4 (Kinase)	Solid Tumors						<ul style="list-style-type: none"> IND-enabling 2021 	

* Currently in Phase 1 dose escalation

Cancer Background and Treatment

Cancer is the second-leading cause of death in the United States. The American Cancer Society estimates that approximately 1.8 million new cancer cases will be diagnosed and more than 600,000 people are expected to die of the disease in the United States in 2020. Cancer is a disease of the genome caused by changes in DNA that alter cell behavior, growth and division. These changes can cause cells to produce abnormal amounts of certain proteins and/or to make aberrant proteins that do not function properly. It is widely understood that cancer cells can eventually evade therapies through mutations or other resistance mechanisms, limiting the long-term success of drug therapies.

Historically, cancer has been treated with surgery, radiation and drug therapy with patients often receiving a combination of these treatment modalities. While surgery and radiation can be effective in patients with localized disease, drug therapies are often required when the cancer has spread beyond the primary site or is not amenable to resection.

Drug therapy is intended to kill or damage malignant cells by interfering with the biological processes that control development, growth and survival of cancer cells. This treatment modality has evolved over time from the use of non-specific cytotoxic therapies to precision oncology medicines targeting molecular pathways or oncogenic drivers. These precision medicines are broadly known as targeted therapies.

Era of Precision Oncology

The first-generation of approved targeted therapies were largely directed at receptor tyrosine kinases (e.g., BCR-ABL, VEGF, EGFR), a superfamily of cell-surface receptors that activate growth factors. Many of these agents that were initially approved in refractory and resistant populations have now become front-line treatments in cancers for which they are indicated. While these targeted therapies have improved the treatment of certain cancers, many fail to address the underlying genomic alterations that drive oncogenesis, leading to limited responses or inadequate therapeutic durability. Since normal cells can rely on these same signaling pathways, there are often toxicities associated with pathway inhibition. In addition, many of these first-generation targeted therapies are multi-kinase inhibitors that interfere with off-target adjacent pathways, resulting in significant toxicities.

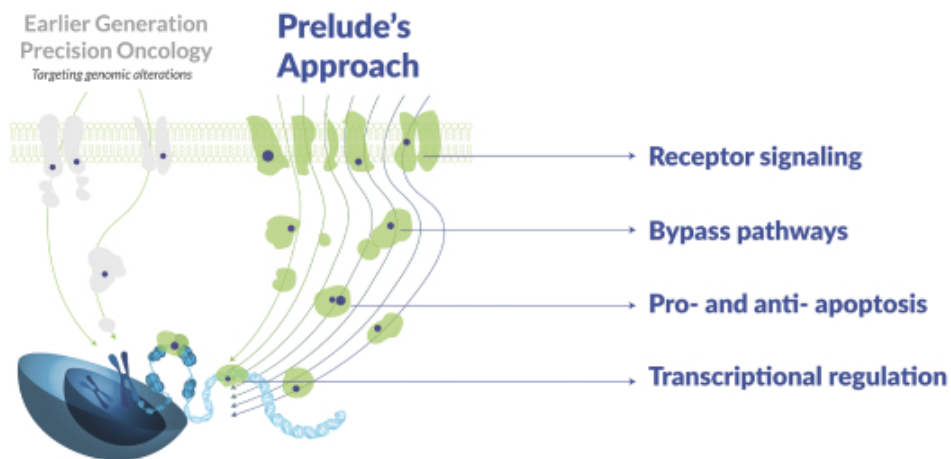
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A second-generation of targeted cancer therapies has evolved from the nexus of rapid advances in the understanding of tumor biology and increasingly sophisticated diagnostic platforms that enable identification of subsets of tumors based on genomic alterations. These therapies often require genomic testing of tumor tissue or blood to identify potentially targetable alterations in a patient’s individual cancer. Increasingly, these precision medicines are agnostic to tumor site of origin and instead target specific oncogenic drivers that can occur broadly across tumor types. In 2018, VITRAKVI (larotrectinib) was approved by the FDA for neurotrophic receptor tyrosine kinase-driven cancers, making it the first new drug to be developed and approved to treat a specific genomic alteration in a tissue-agnostic fashion. This emerging trend for tumor-agnostic indications represents a significant advancement in drug development, clinical trial designs, drug approval patterns and speed to market. Targeted therapies generated approximately \$20.1 billion of worldwide sales in 2019 and have remained a mainstay of oncology drug development and treatment.

Next Generation Precision Oncology

First and second-generation precision oncology medicines dramatically changed the landscape of available treatment options for patients with cancer and created a paradigm shift in oncology drug development. However, there are still significant gaps that require further advances to optimize treatment options. For example, oncology drug development has been primarily focused on readily druggable genomic alterations that confer new or enhanced protein activity, known as gain-of-function targets, which represent only a subset of targets in oncology. Additionally, malignant cells may possess or acquire intrinsic resistance by using alternative signaling pathways, enabling them to survive and proliferate and contributing to a lack of response and/or short durability of response to these types of precision medicines. The nearly universal nature of this primary or secondary resistance highlights the urgent need to address resistance using a cellular level understanding of the mechanisms that drive treatment failure.

By specifically targeting additional pathways of resistance, next generation precision oncology medicines can address the needs of patients whose tumors do not harbor targetable genomic alterations as well as patients who progress on current therapies. These medicines leverage scientific and technological breakthroughs to target new intervention points in oncogenic signaling pathways, including transcriptional regulation of oncogenes and tumor suppressor genes, DNA damage repair pathways and protein structure. These approaches address primary and secondary resistance mechanisms not targetable by earlier generations of precision oncology medicines. Examples of these mechanisms are shown in the figure below.



We believe highly selective and potent molecules that target specific oncogenic mechanisms, regardless of target class, can be an effective strategy to address cancers not amenable to earlier and current treatment

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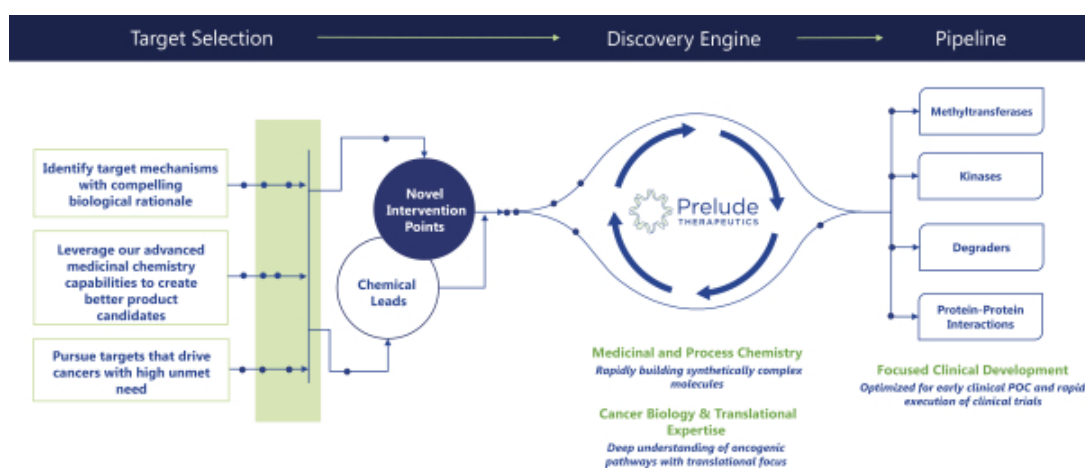
modalities. These next-generation precision therapies should possess pharmacological, pharmacokinetic, or PK, and pharmaceutical properties that provide optimized inhibition of the target mechanism, with a safety profile and therapeutic window that allows use in all stages of cancer either as a monotherapy or in combination.

Prelude Discovery and Development Approach

We are guided by our core expertise in cancer biology and medicinal chemistry to create next generation precision oncology medicines. We endeavor to discover, develop and commercialize small molecule drugs that selectively target signaling pathways driving primary or adaptive resistance.

Our approach is target class- and technology platform-agnostic meaning, we do not limit our selection of programs to a defined target class (e.g., kinases) or a technology platform (e.g., protein degradation). We have built from the “ground up” our internal discovery team, led by scientific and medical teams with deep expertise and proven capabilities in inventing and rapidly advancing small molecule product candidates that have the potential to address important gaps in the current precision oncology ecosystem. We design our discovery programs around targets with compelling preclinical and clinical data that have the potential to address cancers of high unmet medical need. We evaluate existing clinical or preclinical biological rationale and chemical space that provide important “proof-of-concept” validation but present significant opportunities for improvement on current therapies. This process has enabled us to rapidly create a wholly-owned, internally developed pipeline of differentiated product candidates for patient populations with cancers that show limited therapeutic durability or do not respond to current treatments.

As shown in the diagram below, our approach is divided into two related processes—target selection and our unique discovery engine.



Target Selection

We identify vulnerable intervention points in cancers with high unmet need, and then we seek to design solutions that can be precisely tailored to address these in a target class agnostic fashion. Applying our deep expertise in cancer biology and medicinal chemistry, as well as our in-depth understanding of the current landscape of oncology treatments, we interrogate targetable intervention points in the signaling pathways amenable to small molecule-based treatments. We then design, synthesize and optimize molecules that we believe best meet the needs of the patients we strive to serve. Consistent with our patient-centric focus, we take into account a number of patient attributes, including the type of cancer, current standard of care, causes of treatment failure, comorbidities, potential for drug-drug interactions and propensity for CNS disease to be able to develop more effective therapies.

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We carefully evaluate and select our targets based on the three key pillars described below which provide a framework for optimizing our drug discovery and development efforts. Our discovery programs are built upon these three pillars:

1) Identify target mechanisms with compelling biological rationale

We focus on target classes that have either yielded successful drugs or are emerging as validated, druggable approaches with compelling driver pathway-based data, as opposed to approaches driven by disease association or novelty of target class. We believe our internal capabilities are best suited to rationally design and develop molecules that can address these mechanisms in a target class agnostic manner. We may expand our focus on other target mechanisms as new biology emerges and is validated.

Our current target mechanisms of focus include:

- Transcriptional regulation
- DNA repair pathway
- Cell cycle regulation
- Exploitation of synthetic lethality
- Brain penetrant molecules to address primary or metastatic CNS tumors

PRMT5 is a prime example of a target with strong scientific rationale that we are well-suited to address. We believe the target can be exploited to address underserved cancers such as ACC with an undruggable oncogenic driver (such as myeloblastosis, or *MYB*), as well as to address resistance to several existing, approved targeted agents, including ruxolitinib, venetoclax and CDK4/6 inhibitors. Also, *PRMT5* is a potential driver mechanism in GBM, for which a differentiated product with high brain exposure is required.

2) Leverage our advanced medicinal chemistry capabilities to create better product candidates

We deploy our integrated medicinal and process chemistry expertise to rationally design and synthesize complex chemical entities and rapidly advance through various stages of development. We view all target classes, including enzyme inhibitors (*PRMT5*, *CDK9*), protein-protein interactions (*MCL1*), targeted protein degradation (*SMARCA2*) and those that require high levels of brain exposure, with equal interest and strive to invent clinical candidates that meet our desired target product profiles.

Our ability to design and develop molecules with potential high brain exposures allows us to target validated mechanisms in cancers with CNS metastasis, as many current treatments do not have adequate brain exposure. Our discovery programs are not only driven by potency, selectivity and PK, but also incorporate optimized physicochemical properties to provide well-balanced clinical candidates.

3) Pursue targets that drive cancers with high unmet need

We believe taking a patient-centric approach to target selection provides opportunities to generate proof-of-concept early in clinical development, can form the basis for the design of pivotal studies with potential for accelerated approval in the most relevant patient population and rapidly advance into earlier lines of treatment.

We focus on targets that allow us to select patients and cancers with high medical unmet need with no approved therapies, or patient populations underserved by approved treatments. We plan to utilize multiple approaches to patient selection, which include biomarker-based enrichment. For example, one cancer of interest with no approved or effective treatments is ACC, which is predominantly driven by a specific oncogenic mechanism such as *MYB*, where a biomarker selection strategy may not be needed. Alternatively, *SMARCA4* mutated cancers are more amenable to a biomarker-based selection strategy.

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Lastly, we interrogate targets in pathways that drive resistance to approved treatments in clearly defined patient populations. Specific examples include: AML patients who progress on venetoclax in which *MCL1* is a known resistance driver; and patients progressing on ruxolitinib in whom inhibiting PRMT5 can potentially block alternative pathways of resistance such as the transcription factor E2F1.

Our Discovery Engine

Once we have identified optimal targets using the three pillars above, we engage our unique discovery engine to rapidly and efficiently invent and develop molecules with optimized properties. Central to our internal discovery capability is the interplay between our highly experienced biologists and chemists who collaborate in an iterative fashion to rapidly design, synthesize and test novel chemical entities. By coupling our synthetic organic chemistry expertise and analytical technologies, our medicinal chemistry team has rapidly and efficiently synthesized thousands of rationally-designed novel compounds since inception.

Our deep understanding of cancer biology enables a rigorous drug selection process that has allowed us to optimize our lead molecules to interrogate validated cancer pathways with high translational success. We focus on stereochemically-rich molecules with a high degree of 3-dimensional character, which has been shown to correlate with success as compounds transition from discovery, through clinical testing, to drug. Our unique ability to leverage medicinal chemistry to look beyond classic drug-like spaces, such as those involved in protein-protein interaction and targeted protein degradation and to incorporate critical elements of drug-like properties into our candidate compounds is a key aspect of our unique discovery engine. Our internal and external teams utilize a suite of capabilities in crystallography; absorption, distribution, metabolism and excretion, or ADME; PK and pharmacodynamic, or PD, analysis; preclinical efficacy models using cell line xenograft and patient-derived xenograft, or PDX, models; and process scale synthesis and toxicology to evaluate and optimize the lead molecules we invent until they meet rigorous and pre-specified criteria.

Finally, we design our clinical trials to leverage the broad utility of our compounds with a focus on efficient regulatory pathways that enable potentially transformative medicines to quickly reach cancer patients with high unmet medical need. By focusing on validated cancer signaling pathways and early clinical proof-of-concept, we seek to advance our programs through expedited approval processes.

We believe our rapid progress in creating a wholly-owned, internally developed pipeline with three differentiated clinical-development-stage compounds and multiple additional molecules in various stages of preclinical development across a range of target classes validates our discovery excellence. We have structured and resourced our R&D organization with the goal and expectation of continuing to deliver a new IND every 12 to 18 months. We believe our expertise, capabilities and experience to select high value biological targets and invent molecules with an optimized balance of biological and chemical properties differentiates us from others in the precision oncology space.

Our Product Candidates

PRMT5 Inhibitors: PRT543 & PRT811

Rationale for targeting the PRMT5 pathway in cancer

Cancer is a disease of the genome and all cancers have genomic lesions that must be addressed to develop effective treatments. These genomic changes are important at all stages of cancer progression, including initial formation, growth, and metastasis, and result in the upregulation of genes that promote cell growth and survival together with the downregulation of genes that suppress tumor growth.

PRMT5 controls a number of the biological processes that drive cancer including transcription, translation, DNA repair and cell signaling. Overexpression and increased enzymatic activity of PRMT5 are associated with poor outcome and decreased survival in multiple human cancer settings, as outlined in the table below.

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Table 1. PRMT5 Overexpression is Associated with Poor Outcome Across Multiple Cancer Types

<u>Tumor type</u>	<u>Sample Size of Patients</u>	<u>Median Survival (High PRMT5)</u>	<u>Median Survival (Low PRMT5)</u>	<u>Log rank p-value</u>
Ovarian	118	~40 mos*	>80 mos*	0.001
Lung	400	~45 mos*	~75 mos*	<0.0001
Lymphoma	50	~1.6y*	~5.8y*	<0.0001
GBM	43	108 days	726 days	0.0001
Head and Neck	209	~4y*	~10y*	0.012
Pancreatic	55	~15 mos*	~30 mos*	0.015
Colon	90	~34 mos*	~83 mos*	0.02

This information is based on published data in peer-reviewed journals and reflects standard therapeutic intervention.

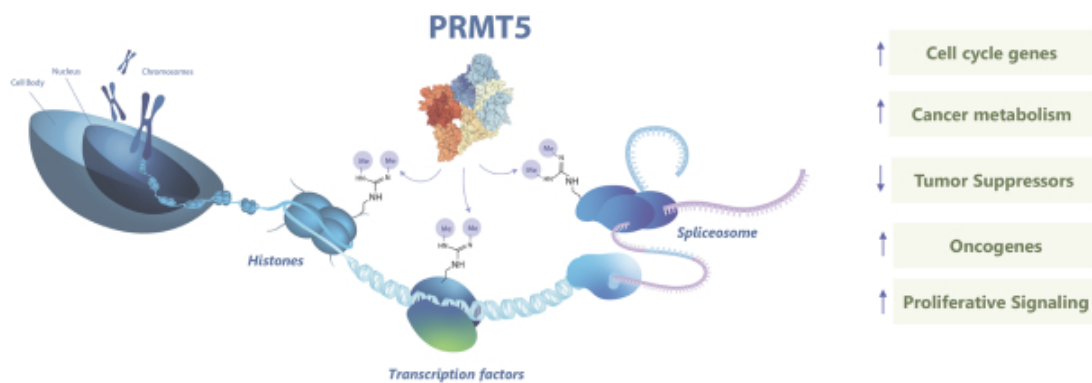
* Where median survival was not explicitly provided in the text, we estimated values from the graphs provided in the publications.

PRMT5 Regulates Transcription and Translation of Cancer-related Genes

The oncogenic process controlled by PRMT5 is mediated through the symmetric dimethylation of arginines on its substrate proteins (Figure 1). PRMT5, an intracellular enzyme, transfers two methyl groups from a co-factor S-adenosyl methionine, or SAM, and deposits them on its substrate proteins resulting in the formation of a symmetric dimethylarginine, or sDMA, mark. This post-translational modification alters the protein structure, impacts interactions with DNA, and also generates docking sites for effector molecules that can promote tumor cell growth and survival. PRMT5 substrate proteins include:

- **Histones**—basic proteins that associate with DNA in the nucleus and help condense it into chromatin
- **Transcription factors**—proteins involved in the process of transcribing DNA into ribonucleic acid, or RNA
- **Spliceosomal proteins**—large protein complex that removes introns from pre-mRNA to yield mature RNA

Figure 1. PRMT5 Regulates Oncogenesis and Resistance



Through arginine methylation of histones, transcription factors and the spliceosome complex, PRMT5 regulates the expression of genes involved in promoting cancer cell growth and survival. These include cell cycle genes, tumor suppressors, oncogenes, and genes involved in proliferation and signaling.

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PRMT5-regulated transcription factors, including cyclin D1 and MYC, have a well-established role in a number of cancers. Conversely, PRMT5-mediated methylation of histones such as H3 and H4 represses a number of tumor suppressor genes including retinoblastoma, or *RB*, family members, contributing to unchecked proliferation of malignant cells. In addition, PRMT5 symmetrically dimethylates ribosomal binding proteins and modulates mRNA translation of internal ribosome entry site-containing mRNAs, further promoting the generation of oncogenic proteins. Consistent with its role in promoting cancer, PRMT5 inhibition has been shown to decrease tumor growth in preclinical models. Therefore, PRMT5 is believed to serve as an important mediator of cancer progression and can be targeted to treat a range of solid tumors and hematological malignancies. These attributes make PRMT5 an ideal therapeutic target for cancer.

The role of PRMT5 in regulating gene transcription and translation may be particularly relevant in cancers such as ACC where up to 86% of patients harbor the gene fusion of the *MYB* family members *MYB* or *MYBL1* with the Nuclear Factor 1B, or *NF1B*, gene. *MYB* or *MYBL1* gene fusions lead to overexpression of the MYB/MYBL1 protein. Published data demonstrate that *MYB* overexpression is important for driving cell proliferation and tumor growth in preclinical ACC models. In addition, our internal data illustrate that PRMT5 inhibition decreased *MYB* expression levels in *MYB*-dependent preclinical models and inhibited tumor growth in PDX models of ACC. Recent evidence of clinical activity with a third party PRMT5 inhibitor in patients with ACC further validates PRMT5 as a potential target mechanism in this highly underserved cancer.

PRMT5 Regulates mRNA Splicing in Cancer Cells

In addition to regulating transcription, PRMT5 also modulates gene expression by controlling mRNA splicing. Splicing is a fundamental cellular process that involves the removal of noncoding sequences from the precursor mRNA to produce the mature form that encodes for protein. In the absence of correct mRNA splicing, mutated or unstable proteins are produced, ultimately leading to cell cycle defects, senescence and apoptosis. The splicing reaction is carried out by a multi-protein/RNA complex called the spliceosome. PRMT5 plays an important role in the splicing of mRNA through methylation of spliceosome protein, which is critical for the assembly of the spliceosome complex and its function. In preclinical models, tumors with high degrees of proliferation, such as *MYC*-driven tumors, were associated with increased activity of PRMT5 to maintain the fidelity of the spliceosome, demonstrating the importance of PRMT5 in this process.

The role of PRMT5 in regulating mRNA splicing may be most relevant in cancers with spliceosomal mutations or those that are dependent on high splicing fidelity, such as GBM. Spliceosomal mutations also occur in more than 50% of MDS patients and at lower frequencies in other tumor types including MF, chronic myelomonocytic leukemia, AML, NHL, MM, chronic lymphocytic leukemia, or CLL, and uveal melanoma. These spliceosomal alterations are often correlated with higher mutational burden and/or poor prognosis. In models of AML, preclinical data demonstrated that PRMT5 inhibition resulted in higher levels of suppression of the growth of cancer cells containing mutated spliceosome proteins compared to those containing unmutated spliceosome proteins.

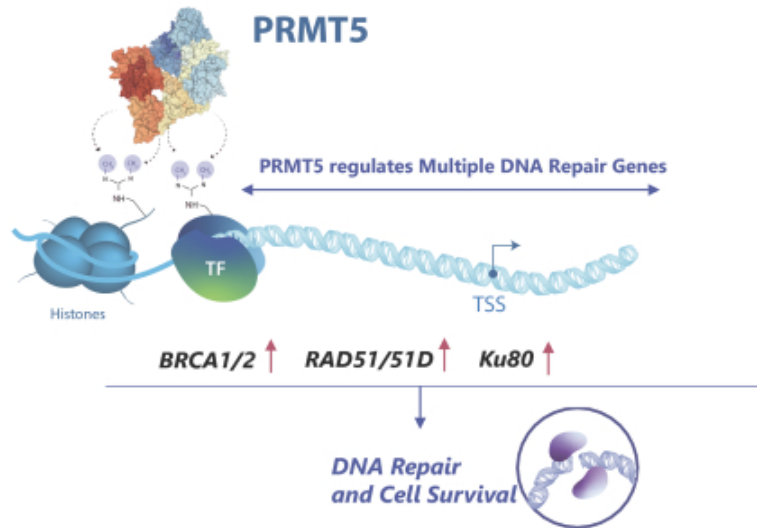
Synthetic lethality from PRMT5 inhibition in certain settings

Synthetic lethality applies to specific pairs of genes. A synthetic lethal interaction occurs when a deficiency in either gene alone is viable whereas a deficiency in both genes simultaneously results in cell death. In cancer, synthetic lethality can be exploited to selectively kill cancer cells in which one gene in the pair is mutated or deleted in the tumor cell and the remaining second gene is therapeutically inhibited. This leads to death of the cancer cells whereas normal cells, which lack the specific genetic alteration, are spared the effect of the drug. In the case of PRMT5, it has been demonstrated that certain genomic alterations confer a selective dependence on PRMT5 so that PRMT5 inhibition can be utilized to produce a synthetic lethal effect. For example, PRMT5 inhibition shows a modest preferential impairment of cell viability in methylthioadenosine phosphorylase, or *MTAP*, -null cancer cells compared to normal cells, suggesting that PRMT5 inhibitors could produce a synthetic lethal effect in GBM, in which nearly half of the patients carry the *MTAP* deletion.

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The synthetic lethal effect of pharmacological inhibitors of DNA repair mechanisms such as poly ADP-ribose polymerases, or PARPs, have been successfully utilized in the treatment of HRD+ cancers. HRD+ can occur as a result of genetic or epigenetic mechanisms that result in loss of genes such as breast cancer genes, or *BRCA1* and *BRCA2*, that are required for efficient DNA repair. More recent data support the potential synthetic lethality of PRMT5 inhibition in tumors that are HRD+ due to the role of PRMT5 in DNA repair (Figure 2). PRMT5 upregulates the transcription of genes involved in HR repair to regulate the DNA damage repair response. PRMT5 inhibition has been shown preclinically to decrease expression of these genes to induce cell death, supporting the potential of PRMT5 inhibitors in HRD+ tumors.

Figure 2. PRMT5 Inhibition in HRD+ Tumors



PRMT5 upregulates the expression of DNA repair genes including *BRCA1*, *BRCA2*, *RAD51*, *RAD51D* and *Ku80*. Inhibition of PRMT5 reduces expression of these genes and prevents DNA repair, inducing a state of "BRCAness" and leading to tumor cell death as well as synergy in combination with PARP inhibitors.

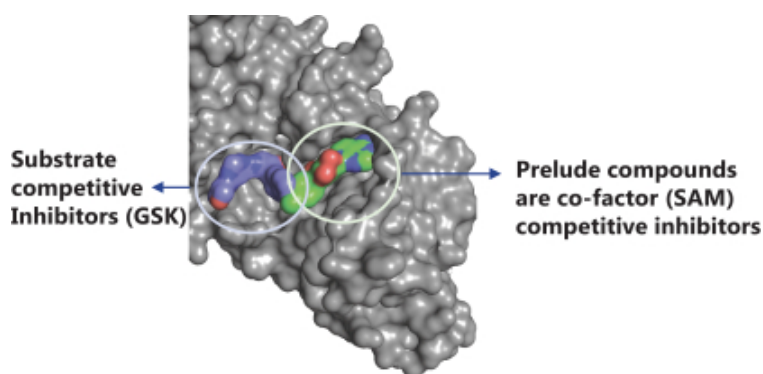
Together, these data support the development of PRMT5 inhibitors in select solid tumors and hematologic malignancies.

Our Approach to Designing Optimized PRMT5 Inhibitors

PRMT5 has strong scientific rationale for its targeting in the treatment of cancer, as its inhibition has been shown to suppress tumor growth and produce synthetic lethality preclinically. PRMT5 contains two binding sites, a substrate and a cofactor (SAM), providing two distinct modes-of-inhibition of PRMT5 (Figure 3). We utilized X-ray crystal structures of PRMT5 to rapidly design and synthesize SAM cofactor mimetic inhibitors that are highly selective for PRMT5, distinct from a substrate competitive inhibitor approach. Given that SAM contributes the methyl group to all of the PRMT5 substrates, we believe this approach gives us an opportunity to more broadly modulate the activity of PRMT5 compared to a substrate competitive inhibitor.

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Figure 3. Binding Mode of Prelude PRMT5 Inhibitors



We rationally designed and synthesized more than 600 compounds during the optimization of our lead product candidates to not only improve potency, but also to simultaneously build in ADME and pharmaceutical properties. These efforts led to selection of our first compound, PRT543, a novel SAM mimetic, that is designed to be a highly potent and selective PRMT5 inhibitor. In addition, to create a PRMT5 inhibitor with the potential for high brain exposure, we optimized the molecular and physicochemical properties of our SAM competitive leads using *in vitro* assays to screen for compounds with low efflux potential followed by confirmatory brain exposure studies *in vivo*. Our second compound, PRT811, is a novel brain penetrant PRMT5 inhibitor. These molecules are differentiated by their mode of inhibition and their potency, which compare favorably to the most advanced PRMT5 inhibitor in development, GSK3326595. PRT543 and PRT811 were selected to advance into clinical development because they have well balanced properties, which we believe will lead to an increase in the probability of clinical activity.

PRT543

Overview

We are currently advancing our first clinical candidate PRT543, an oral inhibitor of PRMT5 in a Phase 1 clinical trial in advanced solid tumors and select myeloid malignancies. Upon establishing a recommended expansion dose, we plan to begin enrolling patients in the expansion portion of the Phase 1 program in select tumor types that are potentially driven by PRMT5 dysregulation. These tumor types include ACC, MF, genomically selected MDS, and genomically selected HRD+ tumors. We began patient enrollment into the solid tumor expansion portion of our ongoing Phase 1 trial during the fourth quarter of 2020 and we expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in 2021. We anticipate collecting clinical results for PRT543 beginning in the first half of 2021. We then plan to initiate interactions with the regulatory authorities regarding the design of pivotal trial(s) to enable potential registration of PRT543. We anticipate presenting initial clinical data from the trial at medical meetings in the second half of 2021.

Preclinical Results—Summary

In vitro, we observed that PRT543 is potent and highly selective in biochemical assays. In cellular assays PRT543 treatment resulted in a dose-dependent reduction in symmetric dimethylation of arginine, or sDMA, levels, a direct readout of PRMT5 activity, in tumor cell lines. PRT543 inhibited the proliferation of a panel of cell lines representative of both hematologic and solid tumor types both as monotherapy and in combination with other targeted therapies. PRT543 was active in cell lines that are resistant to other targeted agents.

In vivo, PRT543 demonstrated high oral bioavailability (F%>100% in rats; 65%, in dogs) and a long half-life (~5-10h in rats and ~20h dogs). PRT543 exhibited activity in a range of xenograft and PDX models of solid

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tumors and hematologic malignancies, including ACC, AML and MF. In these tumor models, PRT543 demonstrated a clear dose-response relationship between suppression of sDMA levels and tumor growth inhibition, or TGI, establishing a link between target engagement and preclinical activity. These data define the target plasma drug concentration and sDMA inhibition goals in the dose escalation portion of human clinical trials.

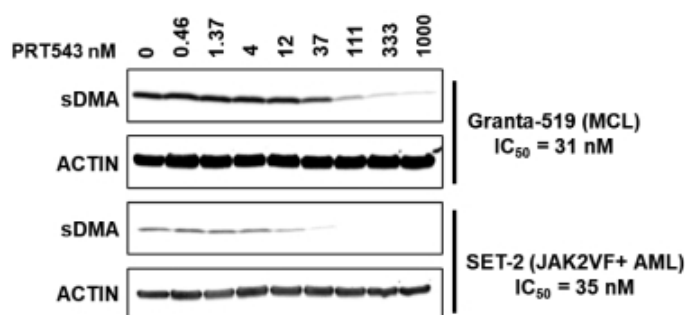
In Vitro Potency and Selectivity

We investigated the *in vitro* potency of PRT543 to inhibit the methyltransferase activity of human recombinant PRMT5 by measuring its IC₅₀. IC₅₀ is a quantitative measure of how much of a compound is needed to inhibit a biological process by 50%. In this assay, we observed the IC₅₀ of PRT543 to be 10.8 nM. We also investigated the *in vitro* selectivity of PRT543 for PRMT5 as compared to a panel of 36 other human methyltransferases. When tested at a concentration 1,000 times above its IC₅₀ for PRMT5, we observed that PRT543 exhibited minimal inhibition of CARM1 (36.5% at 10 μM) and no inhibition of any other human methyltransferase tested.

PRT543 potently reduced sDMA levels, a direct readout of PRMT5 activity, in cells

We determined the potency of PRT543 to inhibit PRMT5 in cells by measuring levels of sDMA, a direct measure of PRMT5 activity. Tumor cell lines were treated *in vitro* with various concentrations of PRT543 for three days and the PRT543 IC₅₀ value to inhibit sDMA determined. We observed that PRT543 potently and dose-dependently reduced sDMA levels in tumor cell lines *in vitro* with nanomolar IC₅₀ values (Figure 4). These data demonstrate on-target effects of PRT543 in cells.

Figure 4. PRT543 Dose-Dependently Reduced sDMA Levels in Tumor Cell Lines *In Vitro*



Western blot demonstrating concentration-dependent reduction of symmetrically dimethylated SMD3, a known PRMT5 substrate, following 3 days of PRT543 treatment in indicated cell lines. Granta-519 is a MCL cell line and SET-2 is a JAK2 V617F mutant AML cell line.

PRT543 inhibits the proliferation of a broad panel of cell lines in vitro

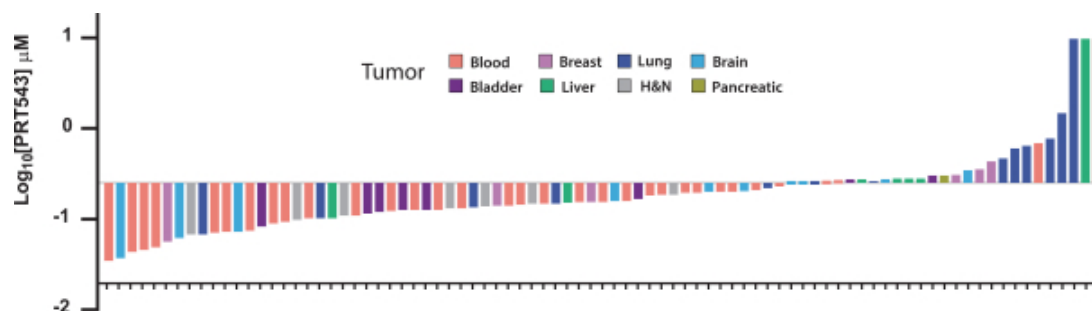
We investigated the potency of PRT543 to inhibit the proliferation of a panel of cell lines representative of both hematologic malignancies and solid tumors *in vitro*. Tumor cell lines were treated with various concentrations of PRT543 and the number of viable cells was measured after ten days in culture. We observed that PRT543 inhibited the growth of cell lines representative of both solid tumors and hematologic malignancies with nanomolar potencies, demonstrating its broad anti-tumor effects *in vitro* (Figure 5).

We also explored whether PRT543 was active in primary cells or cell lines known to be resistant to specific targeted therapies. *In vitro*, we observed that PRT543 inhibited the growth of primary AML patient samples, including those shown to be resistant to the BCL2 inhibitor, venetoclax, or the FLT3 inhibitor, gilteritinib, two currently approved therapies for AML patients. Additionally, PRT543 demonstrated activity in a cell line

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rendered insensitive to JAK inhibitors, suggesting that PRMT5 inhibition may overcome resistance to other targeted therapies.

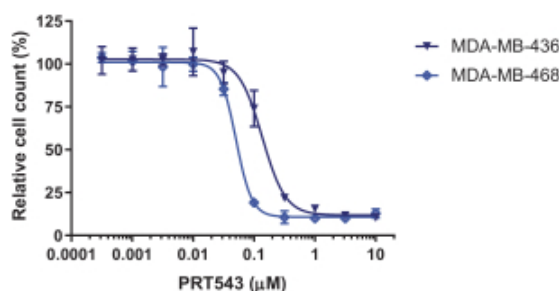
Figure 5: Broad Antiproliferative Activity of PRT543 in a Cancer Cell Line Panel



Profile of the anti-proliferative response to PRT543 in a panel of 85 cell lines following 10 days of treatment. Baseline corresponds to IC₅₀ = 250 nM. Bars below the baseline represent cell lines where PRT543 demonstrates more potent IC₅₀ values and bars above the baseline are less potent.

Given the role of PRMT5 in DNA repair, we investigated the effects of PRT543 to inhibit the growth of HRD+ tumor cell lines. Two HRD+ breast cancer cell lines, MDA-MB-436 and MDA-MB-468, were treated with various concentrations of PRT543 and the number of viable cells was measured after 10 days in culture. We observed that PRT543 demonstrated potent activity in blocking the growth of these cell lines *in vitro* with IC₅₀ values of 50-150 nM (Figure 6). Consistent with this, PRT543 decreased levels of expression of a number of genes involved in DNA repair, including *BRCA1*, *BRCA2*, *ATM* and *ATR*, and was synergistic in combination with PARP inhibitors.

Figure 6. PRT543 Inhibits the Growth of HRD+ Breast Cancer Cell Lines.



Two HRD+ breast cancer cell lines, MDA-MB-436 and MDA-MB-468, were treated for 10 days with PRT543 and effects on cell proliferation determined. Data are plotted relative to DMSO control.

In vivo, PRT543 demonstrated a correlation between sDMA inhibition and efficacy

In vivo, we investigated the ability of PRT543 to reduce sDMA levels in tumor tissues and in plasma in several models, including the SET2 model of AML. PRT543 doses of 5 mg/kg, 15 mg/kg or 30 mg/kg were administered orally to tumor-bearing mice, once daily, for 28 days. As shown in Figure 7, we observed that PRT543 dose-dependently reduced sDMA levels in the tumor, indicating it inhibited cellular PRMT5 activity *in vivo*. PRT543 demonstrated approximately 90% inhibition of sDMA levels in the tumor at the 30 mg/kg and 15 mg/kg once-a-day, or q.d., doses. It should be noted that at doses that result in a 90% reduction in tumor sDMA, approximately 50% reduction in plasma sDMA levels was observed, suggesting that tumor sDMA may be a more

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sensitive readout. PRT543 at both dose levels demonstrated significant anti-tumor activity (Figure 7). Collectively, results from these preclinical models support targeting 50% inhibition of plasma or serum sDMA in Phase 1 dose escalation to establish a pharmacologically active dose.

Figure 7. PRT543 PD/Efficacy Relationship in Preclinical Models

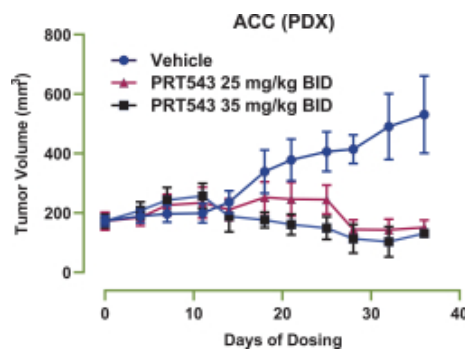


Oral administration of PRT543 leads to dose-dependent decreases in tumor sDMA and TGI in the SET-2 AML model, Western blot showing sDMA reduction in SET-2 tumor tissue collected 4 hours after the last dose, at the end of a 28-day study. Efficacy data represent mean ± SEM with 8 mice/group. * $P < 0.05$, ** $P < 0.01$ vs. vehicle by Mann-Whitney U test.

PRT543 is active in models of ACC and MF in vivo

In vitro, we observed that PRT543 decreased the expression of the *MYB* oncogene as well as *MYB*-regulated genes in head and neck cancer cell lines. Because the activity of the *MYB* oncogene may be important in ACC, where approximately 90% of patients have *MYB* alterations, we investigated whether PRT543 was active in a PDX model of ACC, ACCx9. PRT543 doses of 25 mg/kg and 35 mg/kg were administered orally to tumor-bearing mice, twice daily, for 28 days. We observed that both doses of PRT543 inhibited tumor growth in this PDX model of ACC (Figure 8). These data support the clinical development of PRT543 in ACC.

Figure 8. PRT543 Demonstrated Activity in PDX Models of ACC *In Vivo*

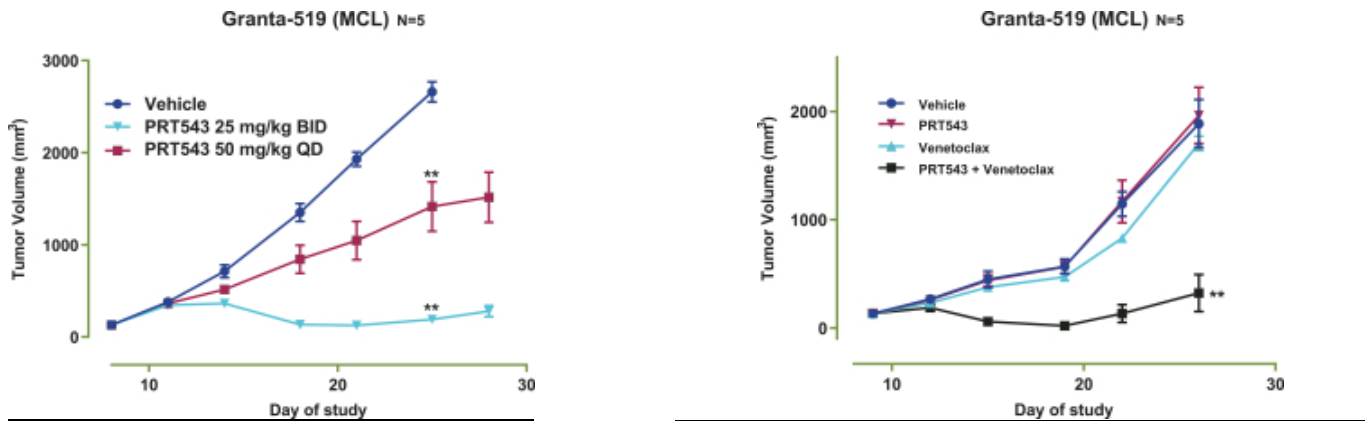


PRT543 oral administration decreased tumor growth in the ACCX9 PDX model of ACC. Data represent mean ± SEM with 8 mice/group.

In addition to studies in ACC models, we observed that PRT543 was active *in vivo* in solid tumor models representative of bladder cancer and small cell lung cancer at well-tolerated doses. PRT543 was also active *in vivo* in models of hematological malignancies, including AML and mantle cell lymphoma. In the Granta-519 model of mantle cell lymphoma, PRT543 demonstrated single agent activity and was synergistic in combination with the approved BCL2 inhibitor, venetoclax (Figure 9).

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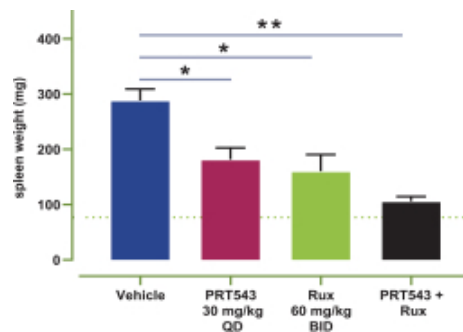
Figure 9. PRT543 is Active as Monotherapy and in Combination *In Vivo*



Oral administration of PRT543 led to dose-dependent TGI in the Granta-519 MCL xenograft model. Combination of PRT543 and venetoclax resulted in significant TGI at doses that did not show activity as monotherapy for both agents in the Granta-519 xenograft model. The doses tested in the combination arm of the study were 20 mg/kg QD of PRT543 and 30 mg/kg QD of venetoclax. Data represent mean ± SEM. ** $P < 0.01$ vs. Vehicle by Mann-Whitney U test.

Finally, we investigated the activity of PRT543 in a model of *JAK2V617F* mutant myeloproliferative neoplasms, or MPN. In this model, we observed that PRT543 led to a reduction in spleen size and normalization of white blood cells and reticulocytes counts, key phenotypic effects of *JAK2* dysregulation through the *JAK2V617F* mutation, both as monotherapy and in combination with the approved JAK inhibitor, ruxolitinib. Importantly, the observed level of suppression of disease specific effects following treatment with PRT543 were similar to those achieved with the approved therapy, ruxolitinib (Figure 10).

Figure 10. PRT543 Was Active in a Model of *JAK2V617F* Mutant MPN.



Oral administration of PRT543 as monotherapy and in combination with ruxolitinib led to significant decrease in spleen size in the *JAK2VF* bone marrow transplant model of MF. Data represent mean ± SEM. Dotted line indicates mean spleen weight of WT transplanted mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. vehicle by Mann-Whitney U test.

Together, these data provide strong rationale for advancing PRT543 into patients with solid tumors such as ACC and HRD+ tumors as well as myeloid malignancies including MF and MDS, and provide opportunities for patient selection (ruxolitinib failures in MF, patients with spliceosomal mutations, HRD+ tumors, *MYB*+ ACC) and combination strategies (with ruxolitinib in MF, venetoclax in MDS/AML, PARP inhibitors in HRD+ tumors).

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Clinical Experience

All data are reflective of a data cutoff of September 1, 2020 unless otherwise stated.

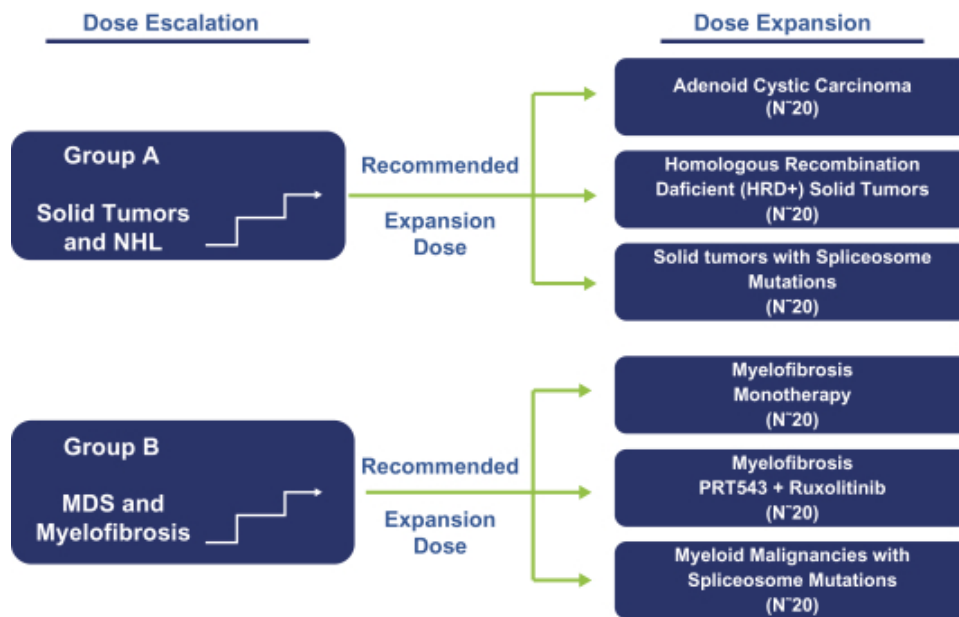
We are currently enrolling a Phase 1, open-label, multicenter, dose expansion clinical trial of monotherapy PRT543 in patients with advanced solid tumors, MF or MDS. We have been encouraged by both the clinical activity and tolerability data that has been observed in 41 patients (29 with advanced solid tumors, one with NHL, nine with MF and two with MDS) that have enrolled into the dose escalation portion of the study as of our data cutoff date of September 1, 2020. We have observed early signs of clinical activity, including a confirmed CR per RECIST v1.1, in a patient with HRD+ high grade serous ovarian cancer, at the 35 mg 5x/week dose level. In addition, one MF patient at the 20 mg twice a week, or b.i.w., dose level has demonstrated a best response of clinical improvement per International Working Group, or IWG, criteria as of September 1, 2020. This patient has exceeded one year on study. A second MF patient at the 40 mg three times a week, or t.i.w., dose level demonstrated an approximately 66% reduction in TSS. Improvement in isolated symptoms and extended duration of therapy have been seen in other MF patients. The safety profile has consisted predominantly of Grade 1-2 adverse events and was similar across both solid tumor and myeloid malignancies patients. As of September 1, 2020, the dose-limiting toxicity experienced at the highest dose level evaluated in both groups has been thrombocytopenia, which in all cases has been reversible without sequelae after a one to two week drug holiday. There have been no deaths or study discontinuation attributed to PRT543. PK/PD analysis reveals dose-dependent increases in drug exposure across doses and schedules with associated decreases in serum sDMA levels. The dose escalation portion of the Phase 1 clinical trial is ongoing, with the dose expansion phase expected to initiate enrollment in the second half of 2020. While early in development and there is no guarantee of approval by the FDA or other regulatory authorities, we are encouraged by the clinical activity of PRT543.

Clinical Trial Design and Schema

Our PRT543 Phase 1 clinical trial design seeks to leverage PRT543's broad potential therapeutic utility to rapidly generate proof-of-concept across multiple solid tumors and myeloid malignancies. Trial enrollment of patients with relapsed/refractory, or R/R, advanced solid tumors, NHL (Group A) or R/R MF or MDS (Group B) commenced in February 2019 and is being conducted at approximately 25 sites throughout the United States. This clinical trial consists of two parts, a dose escalation portion followed by dose expansion into separate tumor-specific cohorts. Enrollment into the dose expansion phase is expected to begin in the second half of 2020. Total expected enrollment is anticipated to be approximately 160 patients. The schema is shown below in Figure 11.

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Figure 11. PRT543 Clinical Trial Schema



Interim and Preliminary Clinical Results

Interim and Preliminary Safety Data: Group A & Group B

The safety profiles of the 41 patients enrolled have been similar between Group A (solid tumor; 30 patients) and Group B (MF and MDS; 11 patients) treated at doses and schedules ranging from 5 mg b.i.w to 50 mg once a day, or q.d.,. Nine patient deaths were reported, none of which were related to PRT543. There were no patients that discontinued study therapy due to an adverse event. A total of 18 SAEs have been reported amongst six patients and of those, only one event (grade 4 thrombocytopenia) in one patient was deemed related to PRT543.

Adverse events were similar between patient groups with the majority of these adverse events (84.6%) being Grades 1-2. The most common adverse events were diarrhea, nausea and fatigue, ranging from 30% to 50% in both groups and were manageable with standard treatment routine amongst patients with cancer.

Dose limiting toxicity of grade 4 thrombocytopenia has been observed in two out of three Group A patients at the 50 mg q.d. dose level and one out of six Group B patients at the 40 mg t.i.w. dose level, one of which was deemed to be a serious adverse event, or SAE. However, in all of these patients, platelets recovered to baseline levels after a one to two week drug holiday and they remained on the study and restarted at a lower dose. At the 35 mg q.d. dose level, three of the four patients have experienced grade 3 thrombocytopenia. Patients had their doses reduced and remained on study. Among the eight patients who either started or were dose reduced to the 35 mg 5x/week dose level, only one experienced any thrombocytopenia (grade 3).

Group A (Solid Tumors)

Pharmacokinetic Data; Group A (Solid Tumors)

Preliminary PK data were available for 30 solid tumor patients administered various regimens of oral doses of PRT543 (mean values are shown in Table 2). We observed that PRT543 demonstrated rapid absorption with the T_{max} generally occurring between one to three hours with dose-proportional increases in exposure. Half-life

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values for different doses ranged from approximately 7-18 hours, consistent with the long half-life predicted by preclinical data. Exposures were generally similar between Day 1 (first dose of cycle) and Day 25 at doses up to 35 mg. However, the 50 mg q.d. dose demonstrated significant accumulation of PRT543, which was likely associated with dose-limiting exposure. The calculated weekly exposure of the 50 mg q.d. dose was >2-fold higher than the 35 mg dose administered 5x/week, with a weekly AUC of 243 $\mu\text{M}\cdot\text{h}$ versus 96 $\mu\text{M}\cdot\text{h}$. Our preliminary PK data showed plasma levels at doses of 22.5 mg and above achieved the concentrations required to inhibit PRMT5 in our preclinical *in vitro* and *in vivo* models, and hence support continued clinical development. We believe our optimal dose will be between 22.5 mg and 50 mg.

Table 2. Preliminary Day 1 Pharmacokinetics in Solid Tumor Cohort

Parameter	Doses and Schedules						
	5 mg (n=1)	10 mg (n=3)	15 mg (n=4)	22.5 mg (n=4)	45 mg (n=5)	35 mg (n=9)*	50 mg (n=4)
	b.i.w	b.i.w	b.i.w	b.i.w	b.i.w.	5x /q.d.	q.d
C _{max} (nM)	52.3	415	525	974	2574	1909	2130
T _{max} (h)	4.0	1.7	2.8	1.8	1.0	1.4	1.6
AUC _{0-t} (nM·h)	617	4540	8060	15860	35410	15120	23200

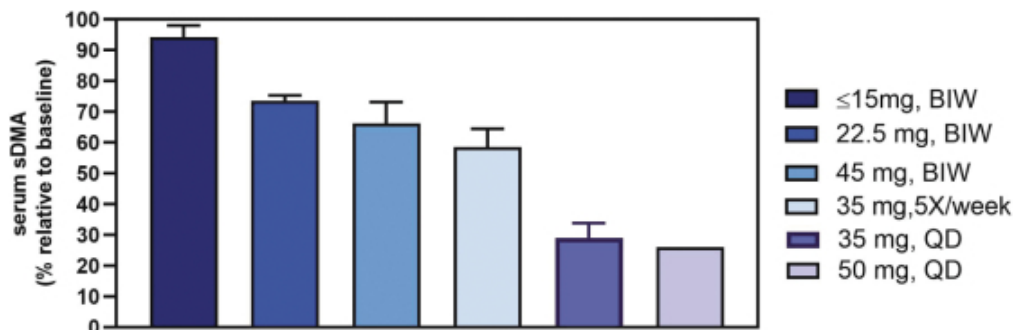
* Day 1 exposure from 35 mg, q.d. and 35mg, 5x dose levels combined. 5x means once a day, for five days, with two days off.

C_{max} means the observed maximum plasma concentration after dosing. T_{max} means the time to reach the C_{max}. AUC_{0-t} means the area under the plasma concentration time curve from time 0 to the last measurable time point.

Pharmacodynamic Data: Group A (Solid Tumors)

Serum sDMA levels, a PD measurement of PRMT5 target engagement, were assessed at baseline and on Day 15 of the treatment cycle. Dose-dependent inhibition of PRMT5 as demonstrated by serum sDMA reduction was observed across groups in the solid tumor cohort. The mean reduction in sDMA level was approximately 75% at both the 35 mg q.d. and 50 mg q.d. doses, which are the highest dose groups evaluated as of September 1, 2020, demonstrating maximum inhibition of PRMT5 activity. In the other cohorts where the dosing was intermittent (b.i.w. and 5x/week doses), serum for sDMA analyses was collected at least 72 hours after the last dose of PRT543 was administered. Therefore, the extent of PRMT5 inhibition was likely underestimated due to rebound in sDMA when the compound is no longer present. In preclinical models, 50% inhibition of sDMA was associated with anti-tumor activity *in vivo*.

Figure 12. PRT543 PD in Solid Tumors



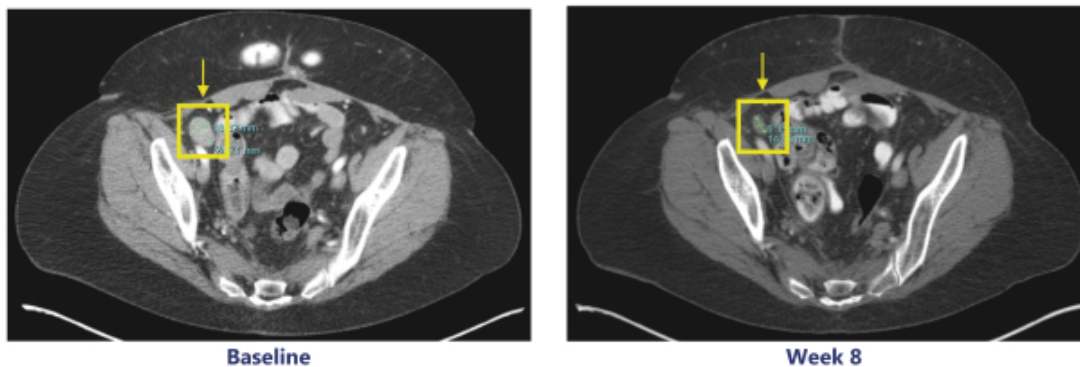
Serum was obtained from patients at various times following administration of PRT543 and analyzed for sDMA levels by LC/MS. The data are shown as % relative to pre-dose levels.

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Interim and Preliminary Efficacy Data: Group A (Solid Tumors/NHL)

Thirty patients have been enrolled into Group A (solid tumors/NHL). Thirteen patients have received doses ³ 35 mg 5x/week and are response evaluable per RECIST 1.1. Of these patients, one patient demonstrated confirmed CR (HRD+ high grade serous ovarian cancer), four patients demonstrated stable disease (including an additional patient with HRD+ ovarian cancer) and four patients showed progressive disease. Seven patients remain on study, of whom four are awaiting their first response assessment. No objective responses were observed in patients that received doses below 35 mg 5x/week. Given that we are still in the dose escalation portion of a Phase 1 clinical trial in a refractory patient population, with the primary objective of evaluating safety and pharmacokinetic properties, and that a majority of patients are likely to be at subtherapeutic doses, we are encouraged by the confirmed CR in the first enrolled biomarker positive patient. The patient, diagnosed in 2014, and subsequently treated with seven prior lines of therapy for metastatic disease, including standards of care such as a PARP inhibitor, as well as experimental therapies, enrolled in the dose escalation portion of the trial at a dose/schedule of 35 mg, 5x/week. Genomic analysis demonstrated mutations in the DNA repair enzymes, *RAD51D*, *ATR*, and *BRCA1*. At baseline, the patient was noted to have one target lesion lymph node, per RECIST, measuring 19mm across the shortest axis. Baseline CA-125 tumor marker levels measured 37.8 U/mL. At the first follow up response assessment, occurring eight weeks after enrollment, the patient's target lesion demonstrated regression to 8mm with an associated drop in CA-125 levels to 2.6 U/mL. At the second follow up scan performed 16 weeks after enrollment, the target lesion regressed in size to 5 mm, confirming the CR. CA-125 levels measured 4.6 U/mL. At the third response assessment, performed 24 weeks after enrollment, the patient's target lesion remained at 5 mm, further supporting the durability of the CR, and CA-125 levels measured 3.3 U/mL. The patient remains on study. Images from the patient's computer tomography scans from baseline and 8 weeks, with highlighted target lesions, are shown below in Figure 13.

Figure 13. Baseline and 8 Week Tumor Assessment CT Scans



Group B (MF and MDS)

Pharmacokinetic and Pharmacodynamic Data: Group B (MF and MDS)

As of the data cutoff, preliminary PK data were available for 11 participants in this cohort (mean values shown in Table 3). As of September 1, 2020, the PRT543 PK profiles have been similar between solid tumor and MF and MDS patients demonstrating rapid absorption and dose-proportional increases in exposure. Exposures were generally similar between Day 1 (first dose of cycle) and Day 25 (last dose of cycle). Our preliminary PK data showed plasma levels at doses of 20 mg and above that achieved the concentrations required to inhibit PRMT5 in our preclinical *in vitro* and *in vivo* models, and hence support continued clinical development.

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Table 3. Preliminary Day 1 Pharmacokinetics in Myeloid Malignancies Cohort

Parameter	Doses and Schedules			
	5 mg (n=1) b.i.w	10 mg (n=1) b.i.w	20 mg (n=2) b.i.w	40 mg (n=7)* b.i.w/t.i.w
C _{max} (nM)	172	486	809	1343
T _{max} (h)	1	1	1.5	1.6
AUC _{0-t} (nM·h)	1120	6150	15750	14888

* Exposures from 40 mg, b.i.w. and t.i.w. dose levels combined.

Similar to the data in the solid tumor cohort, dose-dependent inhibition in sDMA levels was observed in the heme cohort. A maximum inhibition of approximately 40% was observed at the 40 mg doses, but since only intermittent dosing was tested in this cohort, this reduction may be underestimated due to the sample collection 72 hours after the compound was administered.

In addition to changes in sDMA, changes in cytokine levels and other markers of inflammation were measured in the patients in this cohort. Patients with MF have been shown to demonstrate elevated levels of inflammatory markers such as C-reactive protein, serum amyloid A, interleukin-6, tumor necrosis factor, and interleukin-12. PRT543 treatment was associated with reductions in these markers.

Based on the PK and PD data, we anticipate that an additional two to three dose levels, as originally planned, will be required in order to establish a recommended expansion dose in this cohort.

Interim and Preliminary Efficacy Data: Group B (MF and MDS)

Among the 11 patients enrolled into Group B (nine MF and two MDS), all are evaluable for response assessments as per IWG criteria. One MF patient at the 20 mg b.i.w. dose level has demonstrated an objective response of clinical improvement and continues to receive therapy beyond one year to date. A second MF patient at the 40 mg t.i.w. dose level demonstrated an approximately 66% decrease in TSS. Several other MF patients have demonstrated reductions in individual symptoms, notably pruritis, night sweats and fever. Eight patients achieved a best response of SD. We are encouraged by the extended duration of therapy in two additional patients who remained on study for approximately one year.

Clinical Update as of December 16, 2020

As of December 16, 2020, the Phase 1 clinical trial of PRT543 has currently enrolled 61 patients (42 with advanced solid tumors, one with NHL, 11 with MF and seven with MDS). The overall safety profile is unchanged from the September 1, 2020 data cutoff and consistent between both Groups A and B. The majority of drug related adverse events continue to be grade 1-2 with anemia and thrombocytopenia being the most common grade 3-4 adverse events. Thrombocytopenia is the only dose-limiting toxicity. There have been no patients that have discontinued due to adverse events. Amongst the 61 patients, 24 SAEs have been reported amongst 11 patients, with 3 individual SAEs deemed drug related. No drug-related SAEs occurred more than once throughout the study.

We have initiated the ACC expansion cohort of the trial at a dose/schedule of 35mg 5x weekly with the opportunity for intra-patient dose adjustment. Additionally, we have explored both 25mg q.d. and 50mg 5x weekly doses/schedules in the escalation phase, which may enable a dose titration algorithm in expansion. Enrollment into additional solid tumor and myeloid malignancies cohorts is planned in early 2021.

Addressable Oncology Market for PRT543

Our clinical development strategy is to focus first on indications where there is a patient selection strategy along with a high unmet medical need, no approved therapies and opportunity to utilize early clinical data to

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design registrational trials. Based on these criteria, the following are examples of indications where we believe we have significant opportunity. In addition to the indications outlined below, we believe there may be opportunity in additional indications in patients with genomically defined tumors.

Adenoid Cystic Carcinoma (ACC)

Adenoid cystic carcinoma is a malignant tumor of the secretory glands often presenting in the oral cavity and pharynx (e.g., salivary glands), with approximately 1,200 patients diagnosed in the United States each year and 10-15,000 patients living with this cancer in the United States. ACC is characterized by indolent, locally invasive growth with a high propensity for recurrence and distant metastasis. The disease typically follows a slow course, with five-, ten-, and 15-year survival rates after surgical resection of 77.3%, 59.6%, and 44.9%, respectively. However, once ACC becomes metastatic, the prognosis worsens and most patients ultimately die from the disease. ACC affects a relatively young patient population, with a median age at diagnosis of 50-60 years.

The vast majority of patients are initially treated with surgical resection, if possible, followed by radiation. Approximately 40-50% of patients progress to develop advanced or metastatic disease. Chemotherapy and tyrosine kinase inhibitor therapies are the most common systemic therapies for advanced/metastatic disease, yet have shown low response rates and limited durability of disease control in clinical trials. There are currently no approved therapies for the treatment of ACC.

Homologous Recombinant Deficient Tumors (HRD+)

Homologous recombination deficient positive tumors were described for the first time in cancers with germline mutations of the tumor suppressors *BRCA1/2*. Other genetic and epigenetic events can also result in inactivation of various homologous recombination repair components, leading to HRD+ in non-*BRCA1/2* mutated cancers.

Germline *BRCA1/2* mutations resulting in HRD+ occur in 13% and 15% of ovarian and triple negative breast cancers. Furthermore, 50% and 40% of ovarian and TNBC, respectively, are characterized by harboring HRD+ in the absence of germline *BRCA1/2* mutations. Additionally, 10–12% of advanced prostate cancer harbor germline or somatic *BRCA2* inactivation and up to 25% contain a DNA repair defect.

BRCA1/2-mutant cancers are sensitive to PARP inhibitors, a class of drugs that block single-strand break DNA repair, favoring accumulation of double-strand breaks that tumors harboring HRD+ cannot repair. Several PARP inhibitors have been approved for the treatment of HRD+ ovarian, breast, prostate, and pancreatic cancers and generated over \$1.6 billion of revenue in 2019. There are currently no approved therapies for patients who progress on PARP inhibitors.

Myelofibrosis (MF)

Myelofibrosis is part of a group of progressive blood cancers known as MPN. Approximately two-thirds of the 16,000-18,500 MF patients in the United States are classified as intermediate / high risk and are therefore eligible for systemic treatment. MF is associated with significantly reduced quality of life and shortened survival. As the disease progresses and the bone marrow produces fewer red blood cells, patients experience thrombocytopenia (low platelet counts) and anemia (low red blood cell counts) requiring increasing blood transfusions. Patients with MF suffer from multiple physical symptoms including splenic enlargement, excessive sweating, shortness of breath, bone pain, and fatigue. Demonstrated improvement in the Myelofibrosis Symptom Assessment Form TSS, which is comprised of six specific symptoms associated with MF (abdominal discomfort, pain under the left ribs, an early feeling of fullness, night sweats, bone and muscle pain and itching), has served as a key clinical endpoint in MF trials.

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The current standard of care therapy for intermediate- and high-risk MF patients is ruxolitinib, a JAK1/JAK2 inhibitor that inhibits dysregulated JAK. Ruxolitinib revenues in MF were \$1.6 billion in 2019. However, patients with anemia and/or thrombocytopenia are ineligible to receive ruxolitinib. Additionally, most patients will experience disease progression on ruxolitinib within three to five years.

Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes are a group of blood disorders in which bone marrow becomes dysplastic or defective. The affected bone marrow produces aberrant blood cells, resulting in cytopenias (low healthy blood cell counts) that require transfusions. Bone marrow failure is progressive, and in advanced stages of the disease, blasts (immature blood cells) leave the bone marrow and enter the blood stream, leading to AML in approximately one-third of patients.

The American Cancer Society estimates the annual incidence of MDS to be more than 10,000 cases, and studies suggest the prevalence of MDS to be more than 60,000 cases in the United States. Various risk criteria are used to stratify MDS patients, including the French-American-British classifications and the Revised International Prognostic Scoring System, with higher risk MDS patients having a median survival of less than two years. Approximately one-third of MDS patients in the United States are classified as higher risk.

The standard of care treatment for higher risk MDS includes hypomethylating drugs azacitidine and/or decitabine. A significant number of higher risk MDS patients fail or cannot tolerate treatment with azacitidine or decitabine, and almost all patients who initially respond to therapy eventually relapse. Median survival time of MDS patients who have progressed on hypomethylating drugs is less than six months.

Uveal Melanoma (UM)

Uveal melanoma, or UM, is the most common primary intraocular malignancy in adults and comprises 5% of all melanomas. UM is an orphan disease with an estimated annual incidence in the United States and Europe of 6 per million population per year.

Localized treatment for UM, including radiotherapy, phototherapy, and local tumor resection, aims to preserve the eye and vision while preventing metastases. However, surgical removal of the eye can be indicated depending on the tumor size, position, and risk of metastasis. Almost 50% of patients with uveal melanoma will develop distant metastasis. The liver is the most common site of metastasis and is involved in 90% of patients who develop metastatic disease. The median survival of uveal melanoma patients with liver metastases is reported to be five to six months, with a one-year survival of 10% to 15%.

While there have been numerous recent therapeutic advancements and approvals for patients with metastatic cutaneous melanoma, the situation for patients with metastatic uveal melanoma is quite different. Several targeted therapies and immunotherapies have been studied in patients with uveal melanoma; however, response rates have been low (<10%) with median overall survival ranging from 4 to 15 months.

PRT811

Overview

Our second PRMT5 inhibitor, PRT811 is currently advancing in the dose escalation portion of a Phase 1 clinical trial in solid tumors, including GBM and PCNSL. PRT811 is designed to be a highly potent, selective and orally bioavailable molecule optimized for high brain exposure and hence we believe is uniquely positioned to treat PRMT5-sensitive CNS cancers. Upon characterizing PK, PD and safety profile and selecting a recommended dose, we plan to begin enrolling patients, including patients with GBM and other CNS cancers determined to be sensitive to PRMT5 inhibition, in the expansion portion of the clinical trial. We expect these expansions to begin in the first half of 2021 and anticipate initial clinical results from these expansion phases by the end of 2021.

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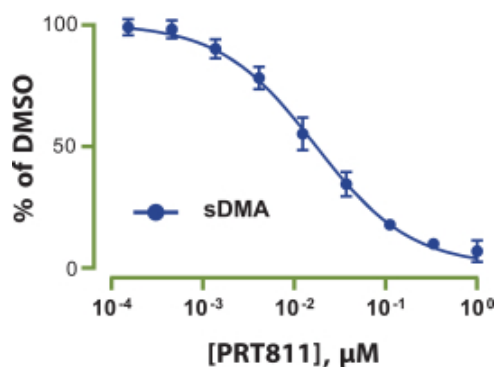
Preclinical

In vitro potency and selectivity

We investigated the *in vitro* potency of PRT811 to inhibit the methyltransferase activity of human recombinant PRMT5 by measuring its IC₅₀. In this assay, we observed the IC₅₀ of PRT811 to be 3.9 nM. We also investigated the *in vitro* selectivity of PRT811 for PRMT5 as compared to a panel of 36 other human methyltransferases. When tested at a concentration >1,000 times above its IC₅₀ for PRMT5, we observed that PRT811 exhibited minimal inhibition of PRMT7 (53.9% at 10 μM) and no inhibition of any other human methyltransferase tested.

We determined the potency of PRT811 to inhibit PRMT5 in cells by measuring levels sDMA, a direct measure of PRMT5 activity. Tumor cell lines were treated *in vitro* with various concentrations of PRT811 for three days and the PRT811 IC₅₀ value to inhibit sDMA determined. We observed that PRT811 potently and dose-dependently reduced sDMA levels in the U87 glioblastoma cell line with an IC₅₀ value of 17 nM (Figure 14). The potency of PRT811 in blocking sDMA levels was confirmed in 11 additional cell lines, with IC₅₀ values in the range of 7-40 nM. These data demonstrate on-target effects of PRT811 in cells.

Figure 14. PRT811 is Highly Selective and Demonstrated Potent Inhibition of sDMA in Cells

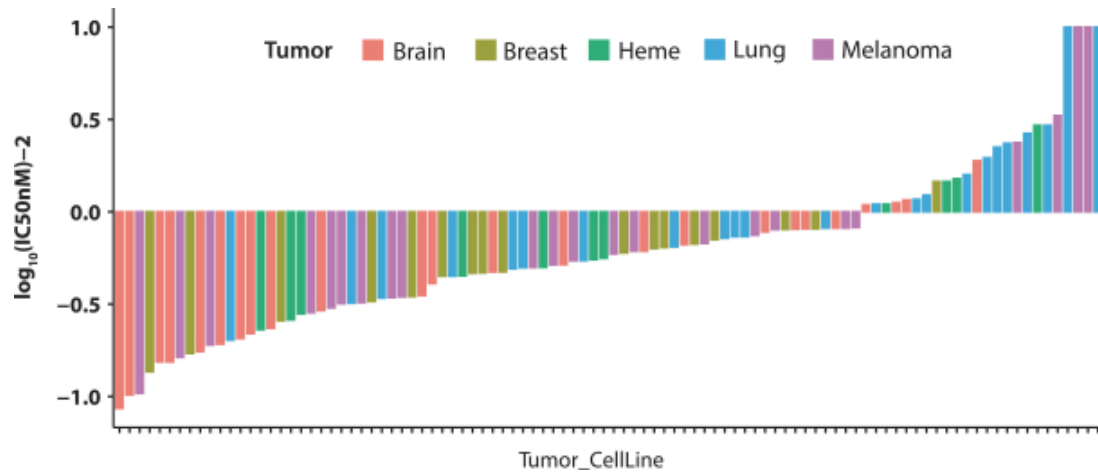


Concentration-dependent inhibition of cellular sDMA by PRT811 in U-87 MG cells following three days of treatment in culture. sDMA IC₅₀=17 ± 1 nM (n=12).

We investigated the potency of PRT811 to inhibit the proliferation of a panel of cell lines representative of brain cancers as well as cancers known to have a high rate of brain metastasis (breast, lung, melanoma and hematological malignancies including lymphoma). Tumor cell lines were treated with various concentrations of PRT811 and the number of viable cells was measured after ten days in culture. Consistent with its effects in blocking sDMA levels, PRT811 inhibited the growth of the majority of cell lines in the panel with nanomolar potencies, demonstrating its broad anti-tumor effects *in vitro* (Figure 15).

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Figure 15. Broad Antiproliferative Activity of PRT811 in a Cancer Cell Line Panel

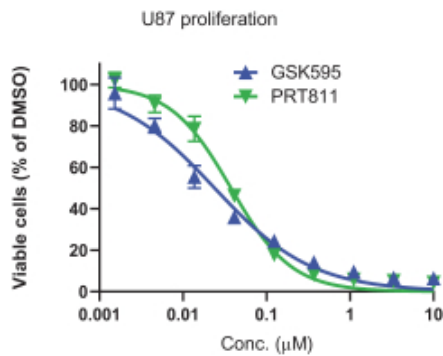


Waterfall plot showing anti-proliferative activity of PRT811 against a panel of 87 cell lines. Cell panel consists of brain cancer cell lines, as well as breast, lung, and melanoma cells lines, the predominant cancer types that metastasize to the brain.

Preclinical pharmacokinetic profile

The PK profile of PRT811 was characterized *in vitro* and *in vivo* in multiple preclinical species including rat, dog and monkey. PRT811 was observed to have good oral bioavailability and high permeability and was not a substrate for P-glycoprotein, or P-gp, and other efflux mechanisms that typically result in low brain exposure. These data suggest PRT811 is not likely to have high efflux out of the brain due to transporters such as P-gp, an important feature of brain penetrant compounds. Accordingly, we observed that the brain exposure of PRT811 in rats after an IV infusion was high with an approximate brain/plasma ratio of two (Table 4). Although both compounds have equivalent potency to inhibit GBM cell line U87 proliferation, the brain:plasma ratio was approximately 100x higher for PRT811 compared to the GSK PRMT5 inhibitor currently in development, providing a clear differentiation for PRT811.

Table 4. Comparison of Cellular Potency and Brain to Plasma Ratio of PRT811 vs. GSK3326595



	GSK595	PRT811
	Mean	Mean
Plasma concentration µmol/L	2.50	2.02
Brain concentration µmol/kg	0.0722	4.11
Brain/plasma ratio	0.0293	2.26

Concentration-dependent inhibition of U87 glioblastoma tumor cell proliferation *in vitro* following 10 days of treatment with PRT811 or GSK3326595. Concentration (total) of PRT811 and GSK3326595 in rat plasma and brain following a 4-h IV infusion at 5 mL/h/kg. Data are expressed as mean concentration (±SD) in naïve male animals (n = 3 per time point).

The ability of a compound to effectively achieve high brain exposures has been highlighted most recently by the significantly improved activity of brain penetrant kinase inhibitors compared to their non-brain penetrant

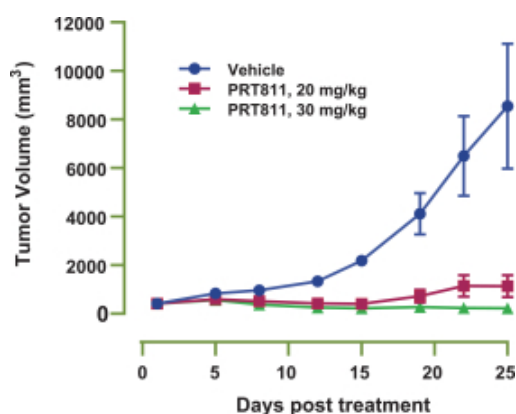
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counterparts in patients with CNS cancers or with CNS metastasis. In addition, a clear role for PRMT5 inhibition in CNS cancers such as glioblastoma has been demonstrated in preclinical models. Glioblastoma has been shown to be highly dependent on correct mRNA splicing for growth and to have alterations in *MTAP* and *cyclin D1*, all markers of enhanced sensitivity to PRMT5 inhibition. High PRMT5 expression has been shown to reduce GBM median survival from over 700 days to approximately 100 days. Together, these data provide a clear rationale for selecting PRT811 for development in CNS cancers.

PRT811 activity in models for GBM

In vivo, we investigated the ability of PRT811 to reduce sDMA levels in tumor tissues in the U-87MG GBM xenograft tumor model. Tumor-bearing mice were dosed orally once daily for 25 days with either 20 or 30 mg/kg of PRT811. PRT811 at both dose levels demonstrated significant anti-tumor activity in the U-87MG model with 91% inhibition at the 20 mg/kg dose and 100% inhibition at the 30 mg/kg dose (Figure 16). At the 20 mg/kg dose, the plasma concentrations of PRT811 were above the protein binding adjusted *in vitro* IC50 value observed in the sDMA cellular assay for approximately six hours, suggesting that continual enzyme inhibition is not required for activity in the model.

Figure 16. PRT811 Inhibited Tumor Growth in the U-87MG Subcutaneous Xenograft Model

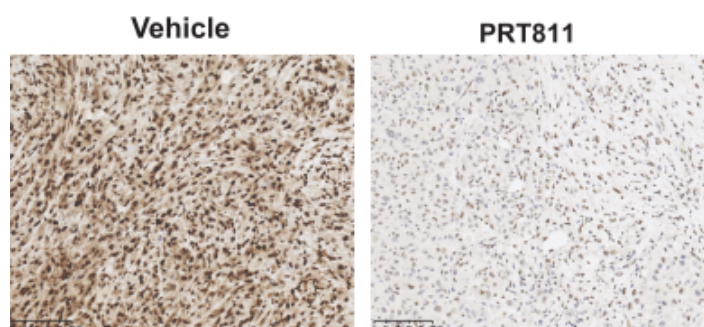


Nude rats bearing subcutaneously implanted U-87 MG tumors were dosed orally with 20 or 30 mg/kg PRT811 q.d. Significant antitumor activities were observed at both doses (tumor regression for 30 mg/kg). *: $P < 0.05$; **: $P < 0.01$. Student's t test, 2 tailed. N=8/arm mg/kg, milligrams/kilogram; PO, oral; q.d., once daily; SEM, standard error of the mean.

Since PRT811 was shown to have brain penetration, the effects of PRT811 treatment on sDMA levels in an orthotopic U-87MG model were also assessed. In this model, the U87 glioblastoma cells were implanted directly in the brain. This model requires compound penetration into the brain in order for the compound to inhibit tumor growth. PRT811 was dosed orally once daily for seven days at 80 mg/kg and sDMA levels measured by immunohistochemistry in the brain tumor tissues. We observed that PRT811 reduced sDMA levels in brain tumor tissues by approximately 50% (Figure 17), indicating that it effectively penetrated the brain tumor tissue and inhibited cellular PRMT5 activity in the brain tumor.

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Figure 17. PRT811 Decreased sDMA Levels in the U87 Orthotopic Model



Mice bearing orthotopic U-87 MG tumors were treated with vehicle or PRT811 (80 mg/kg, BID) for one week. Whole brain sections (FFPE) were stained with H&E or sDMA antibody.

In summary, PRT811 was shown to have high brain exposure, to inhibit PRMT5 activity in a brain tumor model and to demonstrate significant anti-tumor activity *in vivo*. No evidence of CNS toxicity was observed in preclinical toxicology studies. Together, these data support the exploration of PRT811 in cancers, including in GBM, PCNSL and other CNS cancers.

Clinical Experience

All data are reflective of a data cutoff of September 1, 2020 unless otherwise stated.

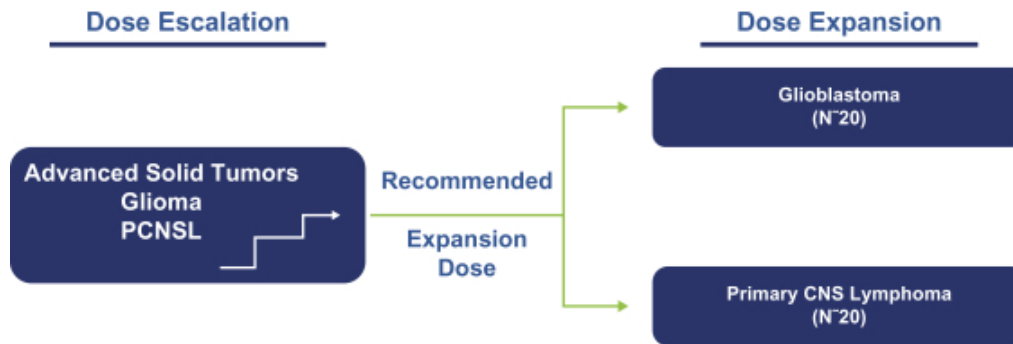
Data is available from 17 patients (ten with solid tumors, six with glioma, one with diagnosis pending) from the dose escalation portion of the ongoing Phase 1 clinical trial of monotherapy PRT811. The safety profile consists predominantly of Grades 1-2 adverse events and was similar across both solid tumor and glioma patients. As of September 1, 2020, no dose limiting toxicities have been seen. PK/PD analysis reveals dose-dependent increases in drug exposure across doses and schedules with associated decreases in sDMA levels. The dose escalation portion is ongoing. The dose expansion portion of the study is expected to begin in the second half of the year.

Clinical Trial Design and Schema

This is a multicenter, open-label, dose-escalation, dose-expansion Phase 1 clinical trial of PRT811. Enrollment into the dose escalation portion of the clinical trial includes patients with R/R solid tumors, PCNSL, and /or high-grade gliomas. Enrollment initiated in November 2019 and is being conducted across seven sites in the United States. We anticipate initiating enrollment of the dose expansion portion of the clinical trial in two patient cohorts consisting of patients with GBM and R/R PCNSL, respectively, in the first half of 2021. The total expected enrollment is approximately 60 patients.

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Figure 18. PRT811 Clinical Trial Schema



Interim and Preliminary Clinical Data

Interim and Preliminary Results: Dose Escalation

As of September 1, 2020, the safety profile among 17 patients demonstrated that PRT811 has been well tolerated at the doses and schedule ranging from 15 mg to 200 mg (q.d. two weeks on/one week off). There were no deaths or study discontinuations related to PRT811. A total of five SAEs have been reported amongst five patients and of those, none were deemed related to PRT811.

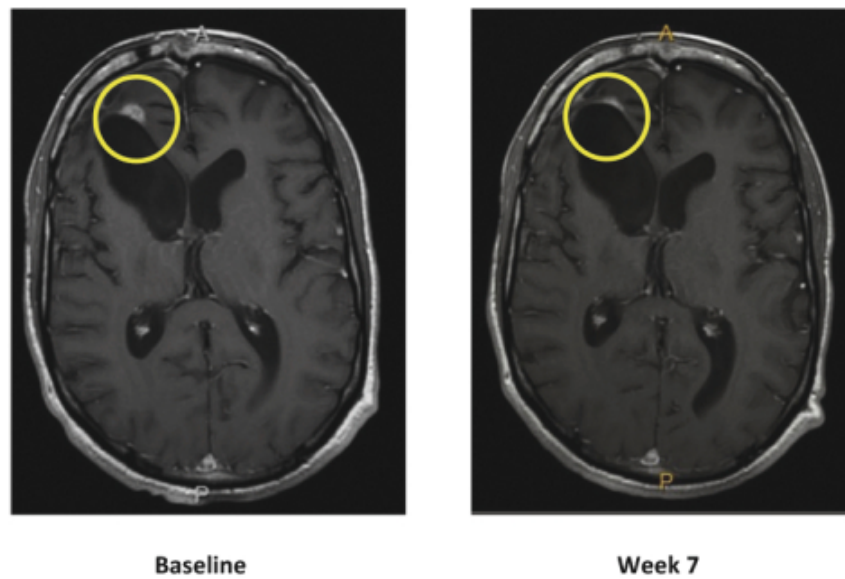
The most commonly reported adverse events, regardless of causality, include constipation (29.4%), nausea (23.5%), vomiting (11.8%) and hyponatremia (11.8%). When examining drug-related adverse events, nausea (17.6%) was most reported. It should be noted that the vast majority, 91.8%, of these adverse events were Grades 1-2 and adverse effects of this type and grade are routine amongst cancer patients and can be medically managed with relative ease.

No dose limiting toxicities have been observed as of September 1, 2020.

Of the 17 patients including six GBM patients evaluated as of September 1, 2020, one patient has demonstrated evidence of tumor size reduction by MRI evaluation. This patient with recurrent GBM, who was originally diagnosed and treated with surgery and chemoradiation with Temodar in July 2019, presented with progressive disease in June 2020. The patient initiated study therapy with PRT811 in July 2020 and was placed into the 200 mg (q.d. two weeks on/one week off) dose cohort. The patient's tumor is positive for IDH1(R132H) mutation and negative for methylation of O6-methylguanine-DNA methyltransferase (MGMT) promoter. Baseline MRI scans revealed a single target lesion, per response assessment in neuro-oncology (RANO) criteria, measuring 23 mm by 10 mm. In September 2020, we were notified that at the patient's first follow-up scan performed on week seven, the lesion measured 13 mm by 6 mm, representing a 66% decrease from baseline. T2/FLAIR (fluid-attenuated inversion recovery) sequence, measured as a standard part of GBM MRI evaluation, was stable. The patient has not been treated with steroids or Avastin and their clinical status is stable. The patient remains on study with follow-up MRI evaluations to be conducted approximately every eight weeks. Figure 18.1 below shows baseline and the first follow up MRI images of the patient's lesion.

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Figure 18.1



Pharmacokinetic and Pharmacodynamic Data

As of the data cutoff, preliminary PK data were available for 17 patients administered PRT811 at one schedule (q.d. two weeks on/one week off). Mean data are shown in Table 5.

We observed that PRT811 demonstrated rapid absorption with dose-proportional increases in exposure. Half-life values for different doses are similar, ranging from two to four hours, as predicted by preclinical data. The maximum plasma concentration, or C_{max}, at the 120 and 200 mg doses reached the estimated IC₅₀ for PRMT5 inhibition. Consistent with the PK, the maximum sDMA inhibition observed, as an indicator of target engagement, was approximately 50% at the 120 and 200 mg dose levels. Based on the current PK and PD, two to three additional cohorts are anticipated, as originally planned, to reach the recommended expansion dose. Our preliminary PK data showed plasma levels at doses of 120 mg and above achieved the concentrations required to inhibit PRMT5 in our preclinical *in vitro* and *in vivo* models, and hence support continued clinical development.

Table 5. Preliminary Day 1 PRT811 Pharmacokinetics

Parameter	Doses				
	15 mg (n=3)	30 mg (n=3)	60 mg (n=3)	120 mg (n=4)	200 mg (n=4)
C _{max} (nM)	34	58	246	530	751
T _{max} (h)	2	2	1.3	1.1	1.0
AUC _{0-t} (nM·h)	100	177	498	1573	1885

Clinical Update as of December 16, 2020

As of December 16, 2020, the Phase 1 clinical trial of PRT811 has enrolled 24 patients (eight with GBM, and 16 with advanced solid tumors). The overall safety profile is unchanged from the September 1, 2020 data cutoff. Four patients have each experienced one SAE, none of which were attributed to study therapy. No dose limiting toxicities have been observed as of December 16, 2020. There has been one patient that has discontinued study therapy due to transient Grade 2 nausea occurring immediately after ingestion of study therapy.

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The 300mg q.d. dose cohort is currently ongoing. We remain on track to complete the dose escalation phase in the first half of 2021 and initiate the expansion phase in cancers including GBM, PCNSL, and CNS metastatic solid tumors in the second half of 2021.

Addressable Oncology Market for PRT811

Our clinical development strategy for PRT811 is to initially focus on CNS indications where there is a patient selection strategy along with a high unmet need, no approved therapies and opportunity to utilize early clinical data to design registrational trials. Based on these criteria, the following are examples of indications where we believe we have significant opportunity. Additionally, we may explore the activity of PRT811 in CNS metastatic disease, which impacts approximately 200,000 patients annually in the United States.

Glioblastoma multiforme (GBM)

Glioblastoma multiforme is the most common malignant primary brain tumor making up 54% of all gliomas and 16% of all primary brain tumors. It is the most aggressive diffuse glioma tumor of astrocytic lineage and under WHO classification is considered a grade IV glioma. Each year, there are approximately 10,000 patients diagnosed with GBM in the United States. GBM remains an incurable tumor with a median survival of only 15 months. Fewer than five percent of GBM patients live beyond five years.

GBMs can be classified into primary and secondary GBMs. Primary GBM occurs de novo without evidence of a less malignant precursor, whereas secondary GBM develops from initially low-grade diffuse astrocytoma (WHO grade II diffuse astrocytoma) or anaplastic astrocytoma (Grade III). The majority of GBMs (90%) are primary and patients with primary GBM tend to be older (mean age = 55 years) than those with secondary GBM (mean age = 40 years).

Treatment is mainly palliative, initially consisting of surgical resection followed by radiation therapy and concurrent chemotherapy. Current therapies include GLIADEL Wafers (carmustine implant), TEMODAR (temozolomide) and AVASTIN (bevacizumab), which show virtually no overall survival benefit for recurrent tumors.

Primary CNS Lymphoma (PCNSL)

Primary central nervous system lymphoma is a type of NHL in which malignant lymphatic cells form in the brain and/or spinal cord. PCNSL can also start in the eye (ocular lymphoma) and/or can involve the cerebrospinal fluid (leptomeningeal lymphoma).

PCNSL is a rare malignancy with an annual incidence rate of seven cases per 1,000,000 people in the United States. PCNSL is relatively more common in immunosuppressed populations, particularly among people with human immunodeficiency virus, or HIV, infection or in solid organ transplant recipients. The median age of diagnosis is 55; the median age of HIV-infected patients with PCNSL is 35.

From 1998 through 2011, survival was poor for PCNSL cases, with just 15.8% of HIV-infected cases and 28.9% of HIV-uninfected cases alive five years after diagnosis. There is no standard treatment for PCNSL, however patients often receive a combination of Rituxan (rituximab), temozolomide, and high-dose methotrexate.

MCL1 Inhibitor: PRT1419

Overview

PRT1419 is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. PRT1419 has been optimized to have the PK properties to allow for either oral or IV administration, providing maximal

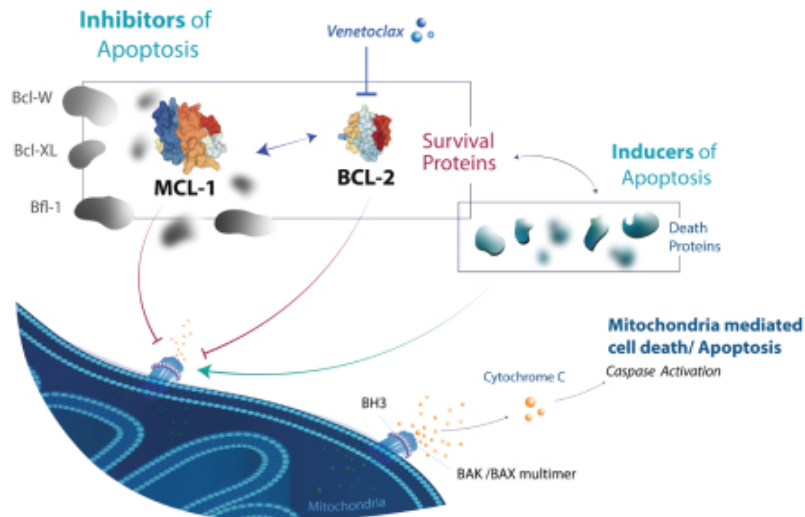
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coverage of the target while maintaining an adequate tolerability window. We have received FDA clearance of our IND to initiate a Phase 1 clinical trial with oral formulation of PRT1419. We have begun enrolling patients into the Phase 1 clinical trial investigating oral PRT1419 in high risk MDS, AML, NHL and MM. Additionally, during the fourth quarter of 2020 we filed an IND for an IV formulation of PRT1419, which we plan to evaluate in various advanced solid tumors. We believe that the physicochemical and pharmacological properties of PRT1419 allow the optionality of administering PRT1419 by either oral or IV route. Based on our preclinical data, as well as published third-party data, we believe that hematological malignancies are particularly sensitive to MCL1 inhibitors. *MCL1* upregulation has been noted as a mechanism of acquired resistance to venetoclax and TKIs. In addition, certain solid tumors are responsive to MCL1 inhibition, informing a potential patient selection strategy. Based on data demonstrating that *MCL1* is a primary resistance mechanism to BCL2 inhibitors like venetoclax, a combination study with azacitidine or venetoclax in MDS/AML is planned. The combination arm is expected to initiate in 2021 after an active dose of PRT1419 as monotherapy has been identified.

Background

The ability to evade cell death is a hallmark of cancer because it is one of the unique acquired abilities that allows malignant transformation of a normal cell. MCL1 and BCL2 are both members of a family of proteins that regulate cell survival versus cell death. Under normal circumstances, MCL1 and BCL2 exert their pro-survival function by binding to and sequestering the pro-death proteins, BAK and BAX, and prevent the activation of a downstream cascade leading to apoptosis (Figure 19). In normal cells, cellular stressors such as DNA damage disrupt this interaction and result in cell death. Cancer cells, however, frequently upregulate pro-survival proteins to prevent activation of the apoptotic pathway, thus evading death. *MCL1* has been shown to have a critical role in promoting cancer cell survival and is frequently found to be amplified or overexpressed in both solid tumors and hematologic cancers.

Figure 19. MCL1 Promotes Tumor Cell Survival by Inhibiting Apoptosis



Members of the BCL2 protein family control cell survival and cell death. MCL1, a member of the family, acts to suppress cell death and has emerged as a target for anti-cancer therapy and as a resistance mechanism to the BCL2 inhibitor, venetoclax.

Inhibition of MCL1 expression and/or function is therefore of considerable therapeutic interest in cancer. The importance of blocking the protein-protein interaction between pro-survival and pro-death proteins as a therapy to promote tumor cell death has been clinically validated with the BCL2 inhibitor, venetoclax. Venetoclax was approved in 2016 for R/R patients with CLL and in 2018 for patients with AML. *MCL1* is

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upregulated in response to BCL2 inhibition and has been implicated in mediating resistance to venetoclax, as well as to chemotherapeutic agents and other targeted therapies including TKIs. These studies have demonstrated the potentially broad clinical benefits of targeting cell survival through MCL1 inhibition in cancer.

Small molecule MCL1 inhibitors have been shown to be remarkably efficacious as monotherapy in preclinical models of MM, AML and lymphoma. Treatment with these inhibitors leads to robust activation of apoptosis markers including cleaved caspase-3 and cleaved PARP *in vivo* and *in vitro*. Objective clinical responses were demonstrated in a Phase 1 multiple myeloma clinical trial with AMG176, a third-party MCL1 inhibitor, providing clinical validation of the pathway. MCL1 inhibitors have also demonstrated potent synergistic activity in combination with approved standard of care therapies, including venetoclax, in preclinical models of AML. Although these inhibitors show limited efficacy as monotherapy in solid tumor models, combination with TKIs has resulted in potent anti-tumor effects in triple negative breast cancer, melanoma and non-small cell lung cancer.

Although the data on the importance of *MCL1* in driving tumor growth and survival are compelling, complete ablation of *Mcl1* has been shown to result in cardiomyocyte apoptosis in mice. Mice with heterozygous deletion of *Mcl1* resulting in a 50% reduction in MCL1 protein did not demonstrate cardiac abnormalities. These results suggest that an optimized profile for a pharmacological inhibitor of MCL1 should allow for maximal but limited duration of target engagement rather than prolonged coverage to maximize the therapeutic window of *MCL1* inhibition in clinical development.

Our Approach to Designing Optimized MCL1 Inhibitors

We used structure-based design to identify PRT1419 as an inhibitor of human MCL1 that is designed to induce tumor cell death by apoptosis. It has been optimized to have high permeability and adequate solubility to provide suitable PK that allows for oral and IV dosing. We believe these features have the potential to maximize the therapeutic window and overcome some of the limitations of current MCL1 inhibitors, as well as provide the convenience and flexibility associated with oral dosing both as monotherapy and potentially in combination with other oral therapies.

PRT1419

In Vitro Potency and Selectivity

We investigated the *in vitro* potency of PRT1419 to inhibit the protein-protein interaction of human recombinant MCL1 with the pro-death protein, BIM, by measuring its IC50. In this assay, we observed the IC50 of PRT1419 to be 6.6 nM. We also investigated the *in vitro* selectivity of PRT1419 for MCL1 as compared to related family members, BCL-2 and BCLXL. We observed that PRT1419 showed >200 times weaker inhibition of BCL-2 and BCLXL compared to MCL1.

Tumor cells undergo apoptosis in response to MCL1 inhibition. Therefore, we investigated the potency of PRT1419 to inhibit the proliferation of cell lines representing both solid tumors and hematologic malignancies. Tumor cell lines were treated with various concentrations of PRT1419 and the number of viable cells was measured after two days in culture. We observed that cell lines representing multiple myeloma, lymphomas and leukemias were particularly sensitive to PRT1419 with IC50 values in the nanomolar range.

Since most MCL1 inhibitors have been shown to be highly bound to proteins in the blood, which reduces their effective concentration, PRT1419 was tested in an assay in the presence of human whole blood and shown to retain its potency to activate markers of apoptosis. In this human whole blood assay, we observed that PRT1419 was significantly more potent (9 times) than other MCL1 inhibitors such as AMG176. Consistent with its improved potency, PRT1419 demonstrated anti-tumor activity *in vivo* at lower doses than those required for activity with AMG176. These data are summarized in Table 6.

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Table 6. *In Vitro* Properties of PRT1419 Compared to Other MCL1 Inhibitors

Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC₅₀ (nM)	150	31	4.5	80
Whole Blood IC₅₀ (nM)	1800	320	430	210
Caco-2 (x10⁻⁶ cm/s)	6	<0.1	0.2	11
Human Hepat. Cl (%HBF)	42	ND	ND	71
Solubility at pH 7.4 (µg/mL)	13	ND	ND	>1000
Route of Administration	IV	IV	IV	Oral/IV

Inhibition of cell proliferation was determined in the OPM2 cell line. Whole blood IC₅₀ represents the half maximal concentration required to induce markers of apoptosis in OPM2 cells cultured in human blood. Permeability was assessed in Caco-2 cells. Intrinsic clearance was determined in human hepatocytes. All competitor compounds were obtained from commercial sources.

Pharmacokinetics

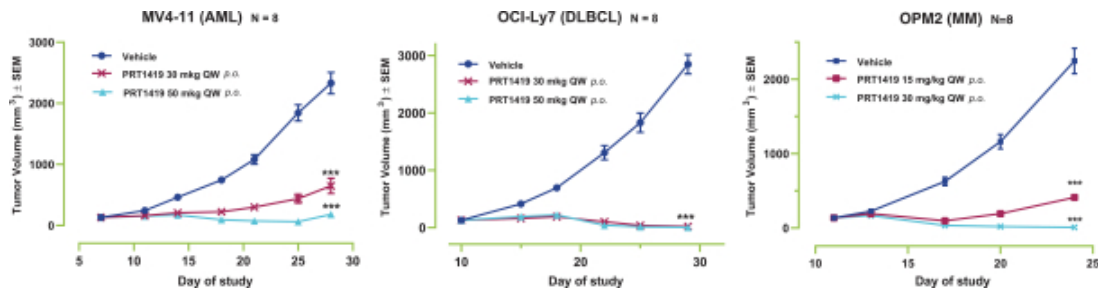
In preclinical assays, PRT1419 demonstrated favorable ADME and PK properties. PRT1419 had high oral bioavailability in mice and dogs, adequate solubility, high permeability, and high intrinsic clearance in human hepatocytes which taken together should favor an optimized PK profile for an oral MCL1 inhibitor in patients.

Anti-tumor Activity in Preclinical Models

In vivo, the pharmacological activity of PRT1419 to induce apoptosis in tumor tissue from the subcutaneous multiple myeloma xenograft tumor model (OPM2) was evaluated. Oral administration of a single dose of PRT1419 led to a dose-dependent activation of apoptosis markers including cleaved caspase-3 and cleaved-PARP in tumor tissue. Consistent with these effects, once weekly administration of PRT1419 demonstrated potent and dose-dependent anti-tumor activity in this model (Figure 20), resulting in tumor regressions. Similar activity was also observed with once weekly dosing of PRT1419 in subcutaneous cell line derived xenograft mouse models of AML (MV4-11) and DLBCL (OCI-Ly7).

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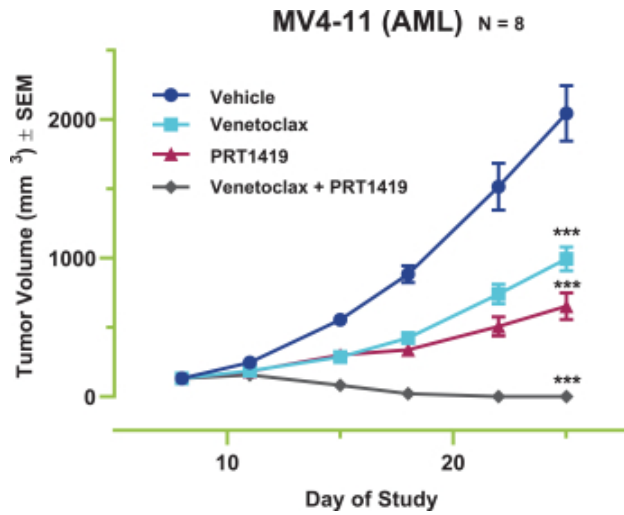
Figure 20. Anti-Tumor Activity in Preclinical Models of Hematologic Malignancies



PRT1419 was administered orally to tumor-bearing mice (n=8 animals/group). Data represents mean ± SEM (standard error of the means), QW – once weekly, p.o – oral administration, *** P value < 0.001 vs. Vehicle by Mann-Whitney U test

Since *MCL1* is known to be a resistance mechanism in patients treated with the BCL2 inhibitor venetoclax, PRT1419 was studied in combination with venetoclax in the MV411 model of AML. As shown in Figure 22, PRT1419 demonstrated enhanced inhibition in combination with venetoclax, resulting in tumor regression in mice.

Figure 21. PRT1419 Demonstrates Enhanced Activity in Combination with Venetoclax



PRT1419 and venetoclax were administered orally as single agents and in combination to tumor-bearing mice (n=8/group). Data represents mean ± SEM (standard error of the means), Venetoclax was dosed at 50 mg/kg; PRT1419 was dosed at 15 mg/kg; *** P value < 0.001 vs. Vehicle by Mann-Whitney U test

In summary, PRT1419 demonstrated potent and selective inhibition of *MCL1* *in vitro* and *in vivo* that resulted in tumor regressions in preclinical models following once weekly oral dosing. PRT1419 was well-tolerated in 28-day toxicology studies in rats and dogs and showed no evidence of cardiac toxicity. Taken together, these studies support the advancement of PRT1419 into clinical trials in patients with hematologic malignancies.

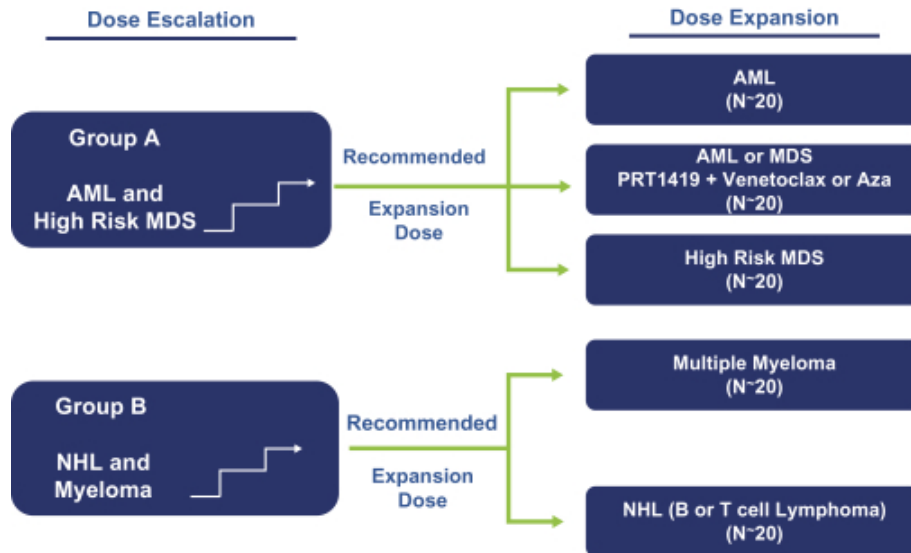
Clinical Trial Design and Study Schema

We are in the process of initiating a multicenter, open-label, dose-escalation, dose-expansion Phase 1 clinical trial of PRT1419. Enrollment into the dose escalation portion of the clinical trial will be conducted across

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two groups; Group A will include patients with either R/R high risk MDS or AML. Enrollment in Group B will include patients with either R/R B Cell or T cell lymphoma or MM. The trial is being conducted across seven sites across the United States. Enrollment is expected to initiate in the second half of 2020. A dose expansion portion of the trial will commence after completion of the dose escalation portion of the trial and will evaluate several select patient dosed with either monotherapy PRT1419 or PRT1419 given in combination with existing standards of care.

Figure 22. PRT1419 Clinical Trial Schema



Clinical Update as of December 16, 2020

As of December 16, 2020, the Phase 1 clinical trial of PRT1419 has enrolled four patients with various hematological malignancies. No adverse events above Grades 1 or 2 and no serious adverse events have been observed.

We are currently enrolling AML and high-risk MDS patients into the second dose escalation cohort (200mg 1x weekly).

Addressable Oncology Market for PRT1419

Acute Myeloid Leukemia (AML)

AML is a blood cancer wherein myeloid stem cells proliferate and fail to properly differentiate into mature myeloid cells. AML is the second most common leukemia in adults, with the American Cancer Society estimating an annual incidence of nearly 20,000 patients in the United States.

AML is particularly difficult to treat in adults older than 60 years, who account for more than 60% of patients; thus, fewer than 29% of AML patients live beyond five years. There are significant differences in the treatment of AML based on age and fitness. For younger, fit patients current first-line AML treatment typically involves aggressive chemotherapy followed by stem cell transplantation if possible. For older, unfit patients first-line AML treatment typically involves low dose cytarabine or azacytidine, potentially in combination with VENCLEXTA (venetoclax) or other agents.

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Other approved therapies for AML include MYLOTARG (gemtuzumab ozogamicin), an antibody-drug conjugate, as well as a number of targeted therapies for subsets of patients whose tumors harbor specific alterations. These include RYDAPT (midostaurin) and XOSPATA (gilteritinib) for FLT3-mutated AML, IDHIFA (enasidenib) for IDH2-mutated AML, and TIBSOVO (ivosidenib) for IDH-1 mutated AML.

Despite these recent advances, we believe there remains a need for a well-tolerated and effective therapy that can broadly address AML patients, especially those progressing on front-line therapies and/or venetoclax. In the registrational study for venetoclax in combination with azacitidine or decitabine, a composite complete remission, or CRC, of 67% was observed, with a response duration of 11.3 months and a median overall survival, or OS, of 17.5 months.

Non-Hodgkin Lymphoma (NHL)

NHL is a group of blood cancers originating in either B-cells (approximately 85% of all NHL) or T-cells (approximately 15% of all NHL). The American Cancer Society estimates the incidence of NHL to be over 77,000 patients annually in the United States.

NHL is characterized into subtypes according to the natural course of disease progression. Aggressive lymphomas, which account for 60% of all NHL cases, progress rapidly. Diffuse large B-cell lymphoma, or DLBCL, is the most common of these aggressive subtypes. Indolent lymphomas, which account for 40% of all NHL cases, progress more slowly with fewer symptoms upon diagnosis. Follicular lymphoma, or FL, is the most common of these indolent subtypes.

The treatment of NHL varies by subtype and can include one or more of the following modalities: chemotherapy, immunotherapy, radiation therapy, stem cell transplantation, targeted therapy, and cell therapy, or CAR-T. Despite recent therapeutic advances and approvals, there remains a high unmet need for new NHL treatments, particularly for more aggressive subtypes and for patients who have progressed on standard therapies. For example, approximately 50% of patients with DLBCL will be refractory to or relapse on standard therapy. The prognosis for patients with DLBCL who relapse is poor, with median survival of less than one year.

Multiple Myeloma (MM)

MM is a blood cancer originating in the bone marrow that is characterized by excess proliferation of aberrant antibody-producing plasma cells. MM is the third most common blood cancer, and the American Cancer Society estimates an incidence of over 32,000 patients annually in the United States. MM is primarily a disease of the elderly and has a five-year survival rate of 54%.

The treatment of MM depends on the aggressiveness of disease and patient fitness. For patients in good health and with active disease, first-line treatment typically involves high-dose chemotherapy followed by stem cell transplantation if possible. For patients who do not achieve a CR or who are not candidates for stem cell transplantation, systemic chemotherapy is indicated. The past two decades have seen significant advances in systemic treatment for MM, including the introduction of immunomodulatory agents, such as REVLIMID (lenalidomide); monoclonal antibodies, such as DARZALEX (daratumumab); and proteasome inhibitors, including VELCADE (bortezomib) and KYPROLIS (carfilzomib). MM therapies generated approximately \$19.4 billion in world-wide sales in 2019.

Despite these therapeutic advances, MM remains incurable. Patients typically receive multiple lines of therapy but ultimately progress. The median OS for patients who are refractory to both an immunomodulatory drug and proteasome inhibitor is only 13 months.

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CDK9 Program

Overview

CDK9 has emerged as an essential regulator of cancer-promoting transcriptional programs, including those driven by *MCL1*, *MYC* and *MYB*. Inhibition of CDK9 is thus an attractive therapeutic approach to produce synthetic lethality in genomically selected cancers. We have applied our internal expertise to design PRT2527 as a potent inhibitor of CDK9 that exhibits high kinome selectivity, PK properties and solubility that we believe may broaden the therapeutic window of CDK9 inhibition. PRT2527 has entered IND-enabling studies, with IND submission expected in 2021.

Background

Cyclin dependent kinases, or CDKs, are a family of closely related serine/threonine kinases that have demonstrated activity in multiple cancers. The first inhibitors of two of the family members, CDK4 and CDK6, gained FDA approval for HR+ metastatic breast cancer in 2015 and are now broadly used. In contrast to CDK4 and CDK6, which regulate cell cycle progression and proliferation, it is now appreciated that other members of the CDK family play important roles in regulating transcription. CDK9 specifically phosphorylates RNA polymerase II to generate mature mRNA. Given its fundamental role in transcription, CDK9 has emerged as a central node in the transcriptional addiction of cancer.

Importantly, inhibition of CDK9 in cancer has been shown to preferentially deplete short-lived transcripts including key anti-apoptotic genes such as *MCL1* and oncogenic transcription factors such as *MYC* and *MYB*. Preclinical evidence demonstrates that CDK9 inhibition represses *MCL1* and thereby overcomes resistance to the BCL2 inhibitor venetoclax. Additionally, preclinical studies suggest that CDK9 inhibition perturbs *MYC*-mediated signaling and produces synthetic lethality in nuclear protein of the testis midline carcinoma, hepatocellular carcinoma and additional solid tumors. Our patient selection strategy in clinical trials would strive to exploit these synthetic lethality relationships by identifying cancers with molecular evidence of *MCL1* and/or *MYC* dysregulation.

Our CDK9 Inhibitor: PRT2527

Although various non-selective CDK9 inhibitors have progressed through clinical development, they have been significantly limited by narrow therapeutic windows due to adverse effects, including bone marrow suppression, nausea and GI effects. We have utilized structure-based design to identify a novel, structurally differentiated series of CDK9 inhibitors. Iterative synthesis and testing of over 600 compounds allowed the identification of PRT2527, which has improved potency and kinase selectivity compared to AZ4573, the most advanced CDK9-selective inhibitor currently in development. The PK and physical properties of PRT2527 are suitable for IV or SC dosing.

In preclinical models, PRT2527 reduced MCL1 and MYC protein levels and was highly active in the MYC-amplified MV4-11 xenograft model at well-tolerated doses. Our preclinical studies suggest that PRT2527 demonstrates high selectivity and high potency, providing opportunity for a wider therapeutic index compared to less selective CDK9 inhibitors.

SMARCA2 targeted degrader program

Background

SMARCA2 (also known as BRM) and its related family member, SMARCA4 (also known as BRG1), are the enzymatic subunits of the SWI/SNF complex that regulates gene expression by allowing the DNA to be accessible for transcription to mature RNA, a process known as chromatin remodeling. *SMARCA4* is mutated in multiple cancers, including 10-12% of NSCLC, resulting in loss of SMARCA4 protein. Because the activity of

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either SMARCA2 or SMARCA4 is required for chromatin remodeling to occur, the *SMARCA4*-deficient cancer cells become highly dependent on SMARCA2 for their survival. Therefore, we believe targeting SMARCA2 in *SMARCA4*-deficient cancers will produce a strong synthetic lethality, resulting in *SMARCA4* mutant tumor cell death while sparing normal cells that express SMARCA4 protein.

Our SMARCA2 Degradation Program

Due to the high homology between SMARCA2 and SMARCA4, there are few structural differences in the binding sites between the two proteins and thus selective SMARCA2 degradation has been a challenge for medicinal chemistry. Targeted protein degradation is a relatively new approach to degrade oncogenic proteins and has been shown to provide selective degradation of highly homologous proteins. A molecule capable of targeting a protein for degradation (degrader) typically contains a binding element to a targeted protein of interest (SMARCA2), a chemical linker and an E3 ligase binding element which allows for the formation of a ternary complex between the target, the degrader and the E3 ligase that induces ubiquitination and subsequent degradation of the targeted protein. Selectivity can be achieved, not only by the selective binding to the target (SMARCA2), but also through the optimization of the unique ternary complexes formed by the target (SMARCA2) versus its homologous protein (SMARCA4).

We used structure-based drug design to identify a novel series of potent SMARCA2 degraders that are outside the typical drug-like chemical space, being significantly larger and structurally more complex. Extensive structure activity relationships generated by the iterative synthesis and testing of >250 compounds as of the date of this prospectus has allowed the identification of specific structural motifs that provide >20-fold selectivity for SMARCA2 degradation over SMARCA4 while maintaining potent SMARCA2 degradation, DC50 < 10 nM. DC50 is a quantitative measure of how much of a compound is needed to inhibit the degradation of a protein by 50%. We have designed our SMARCA2 degraders to be potent and selective to specifically inhibit *SMARCA4*-deficient human NSCLC cell lines and primary patient derived samples. Optimization of the PK and physical properties suitable for oral, IV or SC dosing is on-going with the goal of initiating IND-enabling studies in 2021.

Kinase Program in Solid Tumors

We are evaluating a kinase that has been shown in preclinical studies to be an oncogenic driver in cancer. Genomic alterations in this kinase have been identified in multiple tumor types and these tumors are sensitive inhibitors of this kinase in preclinical models. Current inhibitors of this kinase in development lack optimal PK and biodistribution properties. Our goal is to identify novel, potent, selective, oral inhibitors of this kinase that have an optimized PK profile for clinical development in patients with solid tumors. Optimization of our lead kinase inhibitor, PRT-K4, is ongoing with the goal of initiating IND-enabling studies in 2021.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the compositions of matter of our product candidates, their methods of use, related technology, and other inventions that are important to our business.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, and know-how related to our business, to defend and enforce our patents, to preserve the confidentiality of our trade secrets, and to operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of precision oncology.

As more fully described below, our patent portfolio includes patent families with claims directed to compositions of matter for, and methods of using, compounds PRT543, PRT811, PRT1419, PRT2527, and

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compounds that degrade SMARCA2. A U.S. patent directed to PRT543 has issued and is expected to expire no earlier than August 9, 2038. In addition, a U.S. patent directed to PRT811 has issued and is expected to expire no earlier than March 14, 2039.

In addition to our filings in the United States, we own patent applications that are pending in Australia, Brazil, Canada, China, Eurasia, Europe, Israel, Hong Kong, India, Japan, Korea, Mexico, New Zealand, Ukraine, and South Africa. Included in these applications are claims directed to the PRT543 composition and methods of using the same therapeutically. The patents from these applications, if issued, are expected to expire in August 2038, subject to any disclaimers or extensions.

The patent portfolios for our most advanced programs are summarized below.

PRT543

Our PRT543 patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims, among other things, PRT543, pharmaceutical compositions comprising PRT543, methods of inhibiting PRMT5 using PRT543, and methods of treating certain cancers, including breast and ovarian cancers, using PRT543. This U.S. patent is expected to expire no earlier than August 9, 2038, subject to any disclaimers or extensions available under the Hatch-Waxman Act. Corresponding patent applications are pending in several other countries and regions, including Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, Israel, India, Japan, Korea, Mexico, New Zealand, Ukraine, and South Africa. Any patents resulting from these patent applications, if issued, are also expected to expire no earlier than August 9, 2038, subject to any disclaimers or extensions.

The PRT543 patent portfolio also includes three pending U.S. and two pending PCT patent applications, which claim, among other things, a genus of compounds that encompass PRT543, PRT543 salts and crystalline forms, methods of preparing PRT543, and additional methods of treatment using PRT543. Any U.S. patents issuing from these applications would be expected to expire no earlier than August 9, 2038, February 13, 2040, April 3, 2040, and December 10, 2041 respectively, subject to any disclaimers or extensions.

PRT811

Our PRT811 patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims, among other things, PRT811, pharmaceutical compositions comprising PRT811, methods of inhibiting PRMT5 using PRT811, and methods of treating certain cancers, including glioblastoma, using PRT811. The patent is expected to expire no earlier than March 14, 2039, subject to any disclaimers or extensions available under the Hatch-Waxman Act. A related PCT application was filed, and corresponding national phase applications were filed in Australia, Brazil, Canada, China, Eurasia, Europe, India, Israel, Japan, Korea, Mexico, New Zealand, Ukraine and South Africa. Any patents resulting from these national patent applications, if issued, are expected to expire no earlier than March 14, 2039, subject to any disclaimers or extensions.

The PRT811 patent portfolio also includes two pending U.S. non-provisional applications, a first PCT application that claims compositions of matter, and a second PCT application that claims methods of treatment. Any patents issuing from the two pending U.S. non-provisional applications would be expected to expire in 2039, and any patents issuing from the two PCT applications would be expected to expire in 2040, subject to any disclaimers or extensions.

PRT1419

Our PRT1419 patent portfolio, which is wholly owned by us, includes pending U.S. patent applications claiming, among other things, PRT1419 and other compounds, pharmaceutical compositions comprising PRT1419, and methods of using PRT1419. Any patents issued from this application would be expected to expire

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no earlier than November 8, 2039, subject to any disclaimers or extensions. A related PCT application was filed and national patent applications based on that application are planned for filing in non-U.S. countries in May and June 2021. Any patents resulting from these national patent applications, if issued, would expire no earlier than November 8, 2039, subject to any disclaimers or extensions.

The PRT1419 patent portfolio also includes a pending U.S. provisional application that claims additional compositions of matter. Any patents granted that claim priority to this provisional application could expire as late as 2041.

PRT2527

Our PRT2527 patent portfolio, which is wholly owned by us, includes one U.S. non-provisional patent application and one PCT application claiming, among other things, PRT2527 and other compounds, pharmaceutical compositions comprising PRT2527, and methods of using PRT2527. Any patents that issue based upon these U.S. non-provisional and PCT applications would be expected to expire no earlier than 2040, subject to any disclaimers or extensions.

SMARCA2 Degradars

The SMARCA2 degrader patent portfolio includes one pending non-provisional U.S. application, one PCT application, and two U.S. provisional applications which claim, among other things, genera of compounds that encompass SMARCA2 and/or related inhibitors, pharmaceutical compositions comprising those inhibitors, and methods of treating cancer with those inhibitors.

Other

In addition, we have patent portfolios that are directed to a number of different compounds other than PRT543, PRT811, PRT1419, PRT2527, and SMARCA2 degradars. We have patent applications directed to compounds that target resistance mechanisms in cancer. We expect to maintain some of these applications in the United States and to also file in foreign countries. In addition to the applications described above, we wholly-own 11 applications including U.S. provisional patent applications, U.S. non-provisional patent applications, foreign applications, and PCT applications, covering compositions and methods of making and using those compounds to treat cancer and other diseases.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In the countries in which we file, the patent term is 20 years from the earliest non-provisional filing date, subject to any disclaimers or extensions. The term of a patent in the United States can be adjusted due to any failure of the United States Patent and Trademark Office following certain statutory and regulation deadlines for issuing a patent.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for a portion of the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the original expiration of the patent. The protection provided by a patent varies from country to country, and is dependent on the type of patent granted, the scope of the patent claims, and the legal remedies available in a given country.

Obtaining patent protection is not the only method that we employ to protect our proprietary rights. We also utilize other forms of intellectual property protection, including trademark, copyright, and trade secrets, when those other forms are better suited to protect a particular aspect of our intellectual property. Our belief is that our proprietary rights are strengthened by our comprehensive approach to intellectual property protection. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other

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advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely for the foreseeable future, on third parties for the manufacture of our product candidates for preclinical and clinical testing, including pharmaceutical ingredients and clinical drug supply, as well as for commercial manufacture of any drugs that we may commercialize. We obtain our supplies from these manufacturers on a purchase order basis and do not have long-term supply arrangements in place. We do not own in-house warehouse facilities. We rely on third parties for storage and distribution of drug substance and drug product. We do not currently have arrangements in place for redundant supply for active pharmaceutical ingredients and drug product. As our development programs progress and we build new process efficiencies, we expect to continually evaluate this strategy with the objective of satisfying demand for registration trials and, if approved, the manufacture, sale and distribution of commercial products.

Commercialization

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. If we are successful in obtaining necessary regulatory approval, we may pursue commercialization on our own or seek to collaborate with a third party for commercialization, particularly outside the United States.

The biotechnology and pharmaceutical industries are characterized by the rapid evolution of technologies and understanding of disease etiology, intense competition and a strong emphasis on intellectual property. We believe that our approach, strategy, scientific capabilities, know-how and experience provide us with competitive advantages. However, we expect substantial competition from multiple sources, including major pharmaceutical, specialty pharmaceutical, and existing or emerging biotechnology companies, academic research institutions and governmental agencies and public and private research institutions worldwide. Many of our competitors, either alone or through collaborations, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient enrollment in clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. As a result, our competitors may discover, develop, license or commercialize products before or more successfully than we do.

Competition

We face competition from segments of the pharmaceutical, biotechnology and other related markets that pursue the development of precision oncology therapies optimized to target the key driver mechanisms in cancers with high unmet need. Several biopharmaceutical companies, including Black Diamond Therapeutics, Inc., Constellation Pharmaceuticals, Inc., Kronos Bio, Inc., Repare Therapeutics Inc., Revolution Medicines, Inc., Relay Therapeutics, Inc., and Zentalis Pharmaceuticals, Inc., are developing precision oncology medicines. In addition, we may face competition from companies developing product candidates that are based on targeting pathways of adaptive resistance, including Amgen, AbbVie, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Pfizer, Bayer and Novartis.

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Furthermore, we also face competition more broadly across the oncology market for cost-effective and reimbursable cancer treatments. The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy, biologic therapy, such as monoclonal and bispecific antibodies, immunotherapy, cell-based therapy and targeted therapy, or a combination of any such methods. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates, if any are approved, may compete with these existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates may not be competitive with them. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. As a result, obtaining market acceptance of, and gaining significant share of the market for, any of our product candidates that we successfully introduce to the market may pose challenges. In addition, many companies are developing new oncology therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

With respect to our PRMT5 programs, PRT543 and PRT811, several companies are developing PRMT5 inhibitors with clinical trials ongoing, including GlaxoSmithKline (GSK3326595), Johnson & Johnson (JNJ-64619178) and Pfizer (PF-06939999). For our product candidate PRT1419, other companies are developing MCL1 inhibitors with monotherapy and/or combination trials ongoing, including Amgen (AMG176), AstraZeneca (AZD5991) and Novartis (MIK665). For our preclinical CDK9 program, both AstraZeneca and Bayer have CDK9 programs in Phase 1 clinical trials.

We could see a reduction or elimination in our commercial opportunity if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient to administer, are less expensive or with more favorable labeling than our product candidates. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

FDA Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the Food and Drug Administration, or FDA, The Federal Food, Drug, and Cosmetic Act, or FD&C Act, and other federal and state statutes and regulations govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending NDAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

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Pharmaceutical product development for a new product or certain changes to an approved product in the U.S. typically involves preclinical laboratory and animal tests, the submission to FDA of an investigational new drug application, or IND, which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to FDA as part of the IND.

FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. Imposition of a clinical hold may be full or partial. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board, or IRB, and ethics committee for approval. The IRB will also monitor the clinical trial until completed. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated checkpoints based on access to certain data from the trial.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence of effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a drug demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances, such as where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

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These Phases may overlap or be combined. For example, a Phase 1/2 clinical trial may contain both a dose-escalation stage and a dose-expansion stage, the latter of which may confirm tolerability at the recommended dose for expansion in future clinical trials (as in traditional Phase 1 clinical trials) and provide insight into the anti-tumor effects of the investigational therapy in selected subpopulation(s).

Typically, during the development of oncology therapies, all subjects enrolled in Phase 1 clinical trials are disease-affected patients and, as a result, considerably more information on clinical activity may be collected during such trials than during Phase 1 clinical trials for non-oncology therapies. A single pivotal trial may be sufficient in rare instances to provide substantial evidence of effectiveness (generally subject to the requirement of additional post-approval studies).

The manufacturer of an investigational drug in a Phase 2 or 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access.

After completion of the required clinical testing, an NDA is prepared and submitted to FDA. FDA approval of the NDA is required before marketing of the product may begin in the U.S. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication. The applicant under an approved NDA are also subject to annual program fees. The FDA adjusts the user fees on an annual basis, and the fees typically increase annually.

FDA reviews each submitted NDA before it determines whether to file it and may request additional information. The FDA must make a decision on whether to file an NDA within 60 days of receipt, and such decision could include a refusal to file by the FDA. Once the submission is filed, FDA begins an in-depth review of the NDA. FDA has agreed to certain performance goals in the review of NDAs. Most applications for standard review drug products are reviewed within ten to twelve months; most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The review process for both standard and priority review may be extended by FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission. The FDA does not always meet its goal dates for standard and priority NDAs, and the review process can be extended by FDA requests for additional information or clarification.

FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an outside advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMP requirements. FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA also typically inspects one or more clinical trial sites to ensure compliance with GCP requirements and the integrity of the data supporting safety and efficacy.

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After FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter, or CRL, generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for FDA to reconsider the application, such as additional clinical data, additional pivotal clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, engage in formal dispute resolution or request an opportunity for a hearing. FDA has committed to reviewing resubmissions in two or six months depending on the type of information included. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval.

If, or when, the deficiencies identified in the CRL have been addressed to FDA's satisfaction in a resubmission of the NDA, FDA will issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks to patients. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of an NDA supplement or, in some case, a new NDA, before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Expedited Development and Review Programs

Fast Track Designation

Fast track designation may be granted for a product that is intended to treat a serious or life-threatening disease or condition for which there is no effective treatment and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. The sponsor of an investigational drug product may request that FDA designate the product candidate for a specific indication as a fast track drug concurrent with, or after, the submission of the IND for the product candidate. FDA must determine if the product candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This "rolling review" is available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The

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sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. At the time of NDA filing, the FDA will determine whether to grant priority review designation. FDA will grant such designation if the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Additionally, fast track designation may be withdrawn if FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Accelerated Approval

Accelerated approval may be granted for a product that is intended to treat a serious or life-threatening condition and that generally provides a meaningful therapeutic advantage to patients over existing treatments. A product eligible for accelerated approval may be approved on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large studies to demonstrate a clinical or survival benefit. The accelerated approval pathway is contingent on a sponsor's agreement to conduct additional post-approval confirmatory studies to verify and describe the product's clinical benefit. These confirmatory trials must be completed with due diligence and, in some cases, the FDA may require that the trial be designed, initiated, and/or fully enrolled prior to approval. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Breakthrough Therapy Designation

FDA is also required to expedite the development and review of applications for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new product candidate may request that FDA designate the product candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the product candidate. FDA must determine if the product candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process, providing timely advice to the product sponsor regarding development and approval, involving more senior staff in the review process, assigning a cross-disciplinary project lead for the review team and taking other steps to design the clinical studies in an efficient manner.

Orphan Drugs

Under the Orphan Drug Act, FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States but for which there is no reasonable expectation that the cost of developing and making the product for this type of disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation must be requested before submitting an NDA. After FDA grants orphan drug designation, the identity of the drug and its potential orphan use are disclosed publicly by FDA. Orphan drug

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designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The first NDA applicant to receive FDA approval for a particular active moiety to treat a rare disease for which it has such designation is entitled to a seven-year exclusive marketing period in the U.S. for that product, for that indication. During the seven-year exclusivity period, FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care, or in instances of drug supply issues. Orphan drug exclusivity does not prevent FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Other benefits of orphan drug designation include tax credits for certain research and an exemption from the NDA user fee.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted except that PREA will apply to an original NDA for a new active ingredient that is orphan-designated if the drug is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer.

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity—patent or nonpatent—for a drug if certain conditions are met. Conditions for exclusivity include FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in a manner consistent with the approved labeling.

Adverse event reporting and submission of periodic reports are required following FDA approval of an NDA. FDA also may require post-marketing testing, known as Phase 4 testing, risk evaluation and mitigation strategies, or REMS, and surveillance to monitor the effects of an approved product, or FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control, drug manufacture, packaging and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with FDA and certain state agencies. Registration with FDA subjects entities to periodic unannounced inspections by FDA, during which the Agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

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The Hatch-Waxman Amendments

Orange Book Listing

Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch Waxman Amendments, NDA applicants are required to identify to FDA each patent whose claims cover the applicant's drug or approved method of using the drug. Upon approval of a drug, the applicant must update its listing of patents to the NDA in timely fashion and each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book.

Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredient(s), strength, route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. An approved ANDA product is considered to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, pre-clinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved under the ANDA pathway are commonly referred to as "generic equivalents" to the listed drug and can often be substituted by pharmacists under prescriptions written for the original listed drug pursuant to each state's laws on drug substitution.

The ANDA applicant is required to certify to the FDA concerning any patents identified for the reference listed drug in the Orange Book. Specifically, the applicant must certify to each patent in one of the following ways: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. For patents listed that claim an approved method of use, under certain circumstances the ANDA applicant may also elect to submit a section viii statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents through a Paragraph IV certification, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA-holder and patentee(s) once the ANDA has been accepted for filing by the FDA (referred to as the "notice letter"). The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice letter. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months from the date the notice letter is received, expiration of the patent, the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed, or a decision in the patent case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired. In some instances, an ANDA applicant may receive approval prior to expiration of certain non-patent exclusivity if the applicant seeks, and FDA permits, the omission of such exclusivity-protected information from the ANDA prescribing information.

Exclusivity

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by FDA in any other NDA, that drug receives five years of marketing exclusivity during which FDA cannot receive any ANDA seeking approval of a generic version of that drug unless the application contains a Paragraph IV certification, in which case the application may be submitted one year prior to expiration of the NCE exclusivity. If there is no listed patent in the Orange Book, there may not be a Paragraph IV

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certification, and, thus, no ANDA for a generic version of the drug may be filed before the expiration of the exclusivity period.

Certain changes to an approved drug, such as the approval of a new indication, the approval of a new strength, and the approval of a new condition of use, are associated with a three-year period of exclusivity from the date of approval during which FDA cannot approve an ANDA for a generic drug that includes the change. In some instances, an ANDA applicant may receive approval prior to expiration of the three-year exclusivity if the applicant seeks, and FDA permits, the omission of such exclusivity-protected information from the ANDA package insert.

Patent Term Extension

The Hatch Waxman Amendments permit a patent term extension as compensation for patent term lost during the FDA regulatory review process. Patent term extension, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. After NDA approval, owners of relevant drug patents may apply for the extension. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be reduced for any time FDA determines that the applicant did not pursue approval with due diligence.

The United States Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. However, the USPTO may not grant an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than requested.

The total patent term after the extension may not exceed 14 years, and only one patent can be extended. The application for the extension must be submitted prior to the expiration of the patent, and for patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

FDA Regulation of Companion Diagnostics

If use of an in vitro diagnostic is essential to safe and effective use of a drug product, then the FDA generally will require approval or clearance of the diagnostic, known as a companion diagnostic, at the same time that the FDA approves the drug product. FDA has generally required in vitro companion diagnostics intended to select the patients who will respond to cancer treatment to obtain a pre-market approval, or PMA, for that diagnostic simultaneously with approval of the drug. The review of these in vitro companion diagnostics in conjunction with the review of a cancer therapeutic involves coordination of review by the FDA's Center for Drug Evaluation and Research and by the FDA's Center for Devices and Radiological Health. Approval and clearance of a companion diagnostic also requires a high level of coordination between the drug manufacturer and device manufacturer, if different companies.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to a substantial application fee, which is typically increased annually.

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In addition, PMAs must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, the applicant must demonstrate that the diagnostic has adequate sensitivity and specificity, has adequate specimen and reagent stability, and produces reproducible results when the same sample is tested multiple times by multiple users at multiple laboratories. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also register their establishment(s), including payment of an annual establishment registration fee, and list their device(s) with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Other Healthcare Laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain general business and marketing practices in the pharmaceutical industry. These laws include anti-kickback, false claims, transparency and health information privacy laws and other healthcare laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act, collectively, the ACA, amended the intent element of the federal statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to commit a violation. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Additionally, the ACA amended the federal Anti-Kickback Statute such that a violation of that statute can serve as a basis for liability under the federal civil False Claims Act.

Federal civil and criminal false claims laws, including the federal civil False Claims Act, prohibit any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal

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government, or knowingly making, or causing to be made, a false statement to have a false claim paid. This includes claims made to programs where the federal government reimburses, such as Medicare and Medicaid, as well as programs where the federal government is a direct purchaser, such as when it purchases off the Federal Supply Schedule. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Most states also have statutes or regulations similar to the federal Anti-Kickback Statute and civil False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Other federal statutes pertaining to healthcare fraud and abuse include the civil monetary penalties statute, which prohibits, among other things, the offer or payment of remuneration to a Medicaid or Medicare beneficiary that the offerer or payor knows or should know is likely to influence the beneficiary to order a reimbursable item or service from a particular supplier, and the additional federal criminal statutes created by the Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits, among other things, knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program or obtain by means of false or fraudulent pretenses, representations or promises any money or property owned by or under the control of any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items or services.

In addition, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published on January 25, 2013, impose obligations on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their business associates and their subcontractors that perform certain services involving the storage, use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information. HITECH increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, many state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, and often are not pre-empted by HIPAA.

Further, pursuant to the ACA, the Centers for Medicare & Medicaid Services, or CMS, has issued a final rule that requires certain manufacturers of prescription drugs to collect and annually report information on certain payments or transfers of value to physicians, as defined by such law, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. The reported data is made available in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties. Effective January 1, 2022, reporting on transfers of value provided and ownership and investment interests held during the previous year to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants and certified nurse-midwives will also be required.

We may also be subject to analogous state and foreign anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, or that apply regardless of payor. In addition, several states now require prescription drug companies to report certain expenses relating to the marketing and promotion of drug products and to report gifts and payments to individual healthcare practitioners in these states. Other states prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals.

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Still other states require the posting of information relating to clinical studies and their outcomes. Some states require the reporting of certain drug pricing information, including information pertaining to and justifying price increases. In addition, certain states require pharmaceutical companies to implement compliance programs and/or marketing codes. Several additional states are considering similar proposals. Certain states and local jurisdictions also require the registration of pharmaceutical sales representatives. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties. Additionally, we may also be subject to state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that business arrangements with third parties comply with applicable healthcare laws and regulations involve substantial costs. If a drug company's operations are found to be in violation of any such requirements, it may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, the curtailment or restructuring of its operations, loss of eligibility to obtain approvals from the FDA, exclusion from participation in government contracting, healthcare reimbursement or other federal or state government healthcare programs, including Medicare and Medicaid, integrity oversight and reporting obligations, imprisonment, and reputational harm. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action for an alleged or suspected violation can cause a drug company to incur significant legal expenses and divert management's attention from the operation of the business, even if such action is successfully defended.

U.S. Healthcare Reform

In the United States there have been, and continue to be, proposals by the federal government, state governments, regulators and third-party payors to control or manage the increased costs of health care and, more generally, to reform the U.S. healthcare system. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, in March 2010, the ACA was enacted, which intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms, substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, (i) subjected therapeutic biologics to potential competition by lower-cost biosimilars by creating a licensure framework for follow-on biologic products, (ii) proscribed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs and therapeutic biologics that are inhaled, infused, instilled, implanted or injected, (iii) increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, (iv) established annual nondeductible fees and taxes on manufacturers of certain branded prescription drugs and therapeutic biologics, apportioned among these entities according to their market share in certain government healthcare programs (v) established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (now 70%) point-of-sale discounts off negotiated prices of applicable brand drugs and therapeutic biologics to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs and therapeutic biologics to be covered under Medicare Part D, (vi) expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability, (vii) expanded the entities eligible for discounts under the Public Health program (viii) created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research, and (ix) established a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

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The Trump administration and Congress have, and we expect they will continue to, seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. Since January 2017, the current U.S. presidential administration has issued several executive orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act, among other things, included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate”. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated “Cadillac” tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amended the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress as part of the Tax Cuts and Jobs Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the United States Supreme Court is currently reviewing this case, although it is uncertain when a decision will be made. It is unclear how such litigation and other efforts to repeal and replace the ACA will impact the ACA. There is still uncertainty with respect to the impact the current U.S. presidential administration and the Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the ACA. However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted to reduce healthcare expenditures. United States federal government agencies also currently face potentially significant spending reductions, which may further impact healthcare expenditures. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A joint select committee on deficit reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030 unless additional Congressional action is taken. The CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. Moreover, on January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. If federal spending is further reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and

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enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a \$135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Additionally, on May 11, 2018, the Trump administration laid out the administration's "Blueprint" to reduce the cost of prescription medications while preserving innovation and cures. More recently, President Trump issued five executive orders that are intended to lower the cost of prescription drug products. It is not clear what effect a change in administration would have on these proposals to reduce drug prices or what proposals a new administration would have to reduce drug prices.

On July 24, 2020 and September 13, 2020, President Trump announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. As a result, the FDA also released a final rule on September 24, 2020 providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. HHS also published an interim final rule that establishes an MFN Model for Medicare Part B drug payment. This regulation would substantially change the drug reimbursement landscape as it bases Medicare Part B payment for 50 selected drugs on prices in foreign countries instead of ASP and establishes a fixed add-on payment in place of the current 6 percent (4.3 percent after sequestration) of ASP. The MFN drug payment amount is expected to be lower than the current ASP-based limit because U.S. drug prices are generally the highest in the world. Although the MFN payment methodology is scheduled to begin on January 1, 2021, it faces uncertain prospects for implementation. Among other things, a change in administration or litigation challenging the regulation could delay or halt its implementation.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

It is possible that additional governmental action is taken to address the COVID-19 pandemic. For example, on April 18, 2020, CMS announced that qualified health plan issuers under the ACA may suspend activities related to the collection and reporting of quality data that would have otherwise been reported between May and June 2020 given the challenges healthcare providers are facing responding to the COVID-19 virus.

Additionally, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA authorization under an FDA expanded access program; however, manufacturers are not obligated to provide investigational new drug products under the current federal right to try law.

Coverage and Reimbursement

Patients in the United States and elsewhere generally rely on third-party payors to reimburse part or all of the costs associated with their prescription drugs. Accordingly, market acceptance of our drug products is

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dependent on the extent to which third-party coverage and reimbursement is available from government health administration authorities (including in connection with government healthcare programs, such as Medicare and Medicaid in the United States), private healthcare insurers and other healthcare funding organizations. Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we may obtain regulatory approval. Coverage decisions may not favor new drug products when more established or lower-cost therapeutic alternatives are already available. Patients are unlikely to use our products unless reimbursement is adequate to cover all or a significant portion of the cost of our drug products.

Coverage and reimbursement policies for drug products can differ significantly from payor to payor as there is no uniform policy of coverage and reimbursement for drug products among third-party payors in the United States. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time-consuming and costly which will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage or adequate reimbursement will be obtained. It is difficult to predict at this time what government authorities and third-party payors will decide with respect to coverage and reimbursement for our drug products. Additionally, we may develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. We, or our collaborators, if any, will be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved.

The market for our product candidates will depend significantly on access to third-party payors' drug formularies or lists of medications for which third-party payors provide coverage and reimbursement. Competition to be included in such formularies often leads to downward pricing pressures. In particular, third-party payors may refuse to include a particular reference listed drug in their formularies or otherwise restrict patient access to a reference listed drug when a less costly generic equivalent or other alternative is available.

The U.S. government, state legislatures and foreign governmental entities have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and coverage and requirements for substitution of generic products for branded prescription drugs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could exclude or limit our drugs products from coverage and limit payments for pharmaceuticals.

In addition, we expect that the increased emphasis on managed care and cost containment measures in the United States by third-party payors and government authorities to continue and will place pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Human Capital

Employees

As of December 16, 2020, we had 68 full-time employees. Women represent approximately 40% of our employees with approximately 31% holding senior management level/leadership roles. Of these employees, 36 have an M.D. or a Ph.D. From time to time, we also retain independent contractors to support our organization. None of our employees are represented by a labor union or covered by collective bargaining agreements, and we believe our relationship with our employees is good.

Diversity & Inclusion

We are committed to creating and maintaining a workplace free from discrimination or harassment on the basis of color, race, sex, national origin, ethnicity, religion, age, disability, sexual orientation, gender

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identification or expression or any other status protected by applicable law. Our management team and employees are expected to exhibit and promote honest, ethical and respectful conduct in the workplace. All of our employees must adhere to a code of conduct that sets standards for appropriate behavior and are required to attend annual training to help prevent, identify, report and stop any type of discrimination and harassment. Our recruitment, hiring, development, training, compensation and advancement at our company is based on qualifications, performance, skills and experience without regard to gender, race and ethnicity.

Competitive Pay & Benefits

We strive to provide pay, comprehensive benefits and services that help meet the varying needs of our employees. Our total rewards package includes competitive pay; comprehensive healthcare benefits package for employees, with family member healthcare benefits covered at 80%; a health savings account with company contribution; 20 days of paid time off and paid holidays; family medical leave and flexible work schedules. In addition, we offer every full-time employee, both exempt and non-exempt, the benefit of equity ownership in the company through stock option grants and our employee stock purchase plan. We sponsor a 401(k) plan and we are in the process of implementing a discretionary matching contribution.

Employee Development & Training

We focus on attracting, retaining, and cultivating talented individuals. We emphasize employee development and training by providing access to a wide range of online and instructor led development and continual learning programs. Employees are encouraged to attend scientific, clinical and technological meetings and conferences and have access to broad resources they need to be successful.

Safety

The safety, health and wellness of our employees is a top priority. In response to COVID-19, we have implemented a safety protocols including shift work scheduling to reduce number of people in the facility, requirements for the wearing of masks and for social distancing, increased cleaning procedures and readily available hand sanitizer. These protocols are designed to comply with health and safety standards as required by federal, state and local government agencies, taking into consideration guidelines of the Centers for Disease Control and Prevention and other public health authorities. In addition, we have provided work-at-home arrangements for employees who are able to do so.

Properties and Facilities

Our principal executive office is located in Wilmington, Delaware where we license a total of approximately 19,800 square feet of office and laboratory space that we use for our administrative, research and development and other activities. The license expires on December 31, 2022 and we have an option to renew the license for an additional 12 months thereafter. We also have a right of first offer in connection with certain licensable additional space in this building that becomes vacant prior to October 31, 2021.

Additionally, we have a development and operations office located in Wilmington, Delaware where we lease a total of approximately 5,000 square feet of office space. The lease under this building expires on March 31, 2021. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Legal Proceedings

From time to time, we may be involved in legal proceedings arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of management, would have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us due to defense and settlement costs, diversion of management resources, negative publicity and reputational harm, and other factors.

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MANAGEMENT

Executive Officers and Directors

The following table provides information, including ages as of November 30, 2020, regarding our executive officers and directors:

<u>Name</u>	<u>Age</u>	<u>Position</u>
Executive Officers:		
Kris Vaddi, Ph.D.	55	Chief Executive Officer and Director
Brian Piper, M.B.A.	49	Chief Financial Officer
David Mauro, M.D., Ph.D.	55	Chief Medical Officer
Peggy A. Scherle, Ph.D.	59	Chief Scientific Officer
Andrew P. Combs, Ph.D.	54	Executive Vice President and Head of Chemistry
Deborah Morosini, M.D.	62	Executive Vice President and Chief of Clinical Affairs
Christopher Pierce, M.B.A.	40	Executive Vice President and Chief of Business Operations
Non-Employee Directors:		
Paul A. Friedman, M.D.	77	Chairman of the Board, Director
David Bonita, M.D.	45	Director
Mardi C. Dier	56	Director
Kelvin Neu, M.D.	46	Director
Victor Sandor, M.D.C.M.	54	Director

Executive Officers

Krishna (“Kris”) Vaddi, Ph.D. has served as our Chief Executive Officer and a member of our board of directors since February 2016. From June 2014 to June 2016, Dr. Vaddi also served as Chief Executive Officer of Orsenix, LLC, a clinical stage biotechnology company. Dr. Vaddi previously held several roles at Incyte Corporation, most recently as Senior Advisor from June 2015 to June 2016 and Group Vice President from March 2010 to June 2015. Dr. Vaddi received a BVSc in Veterinary Medicine from Acharya N.G. Ranga Agricultural University in India and a Ph.D. in Pharmacology and Toxicology from the University of Florida. We believe that Dr. Vaddi’s experience as our founder and Chief Executive Officer and history in the biopharmaceutical field qualifies him to serve on our board of directors.

Brian Piper, M.B.A. has served as our Chief Financial Officer since July 2019. Mr. Piper previously served as Chief Financial Officer and Corporate Secretary at Aevi Genomic Medicine, Inc., a biopharmaceutical company (later acquired by Cerecor, Inc.), from February 2016 until May 2019. Prior to his time at Aevi, Mr. Piper served as Vice President Finance & Investor Relations at Medgenics, Inc., a biotechnology company from April 2014 until January 2016. Prior to that, Mr. Piper served in several roles at Shire Pharmaceuticals plc (later acquired by Takeda Pharmaceutical Company Limited), most recently in Business Development from January 2010 until March 2014. Mr. Piper received a B.B.A. in Finance from the University of Notre Dame and an M.B.A. from the Robert H. Smith School of Business at the University of Maryland.

David Mauro, M.D., Ph.D. has served as our Chief Medical Officer since May 2019. Dr. Mauro previously served as Chief Medical Officer at Checkmate Pharmaceuticals Inc., a biopharmaceutical company, from February 2016 until April 2019. Prior to that, Dr. Mauro served as Chief Medical Officer at Advaxis, Inc. from October 2014 until February 2016. Dr. Mauro served as Executive Director at Merck from 2007-2014 and prior to that he was Director at Bristol Myers Squibb. Dr. Mauro received a B.S. in Biochemistry from Cornell University and an M.D. and Ph.D. from Temple University School of Medicine.

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Peggy A. Scherle, Ph.D. has served as our Chief Scientific Officer since April 2018. Dr. Scherle previously held several roles at Incyte Corporation, a pharmaceutical company, most recently as Group Vice President, Discovery Biology and Preclinical Pharmacology from March 2017 until March 2018. Her prior roles at Incyte included Vice President, Preclinical Pharmacology from 2014 until 2017 and as Executive Director, In Vitro Biology from 2011 until 2014. Earlier in her career, Dr. Scherle held scientific research positions with DuPont Pharmaceuticals and Bristol-Myers Squibb. Dr. Scherle received a B.S. degree in Biochemistry from Michigan State University and a Ph.D. in Immunology from the University of Pennsylvania. She completed her postdoctoral training at the National Institutes of Health.

Andrew P. Combs, Ph.D. has served as our Executive Vice President and Head of Chemistry since April 2019. Dr. Combs previously held several roles at Incyte Corporation, a pharmaceutical company, most recently as Vice President of Discovery Chemistry where he led teams in medicinal chemistry, analytical chemistry, enabling technologies, computational design and informatics from January 2003 until February 2019. His prior roles at Incyte included as Senior Director from 2003 until 2006 and as Executive Director from 2006 until 2015 and Vice President from 2015 until 2019. Earlier in his career, Dr. Combs held positions of increasing responsibility, starting as a Senior Research Scientist and advancing to a Director of medicinal chemistry at DuPont-Merck, DuPont Pharmaceuticals and Bristol-Myers Squibb. Dr. Combs received B.S. degrees in Chemistry and Molecular Biology from the University of Wisconsin-Madison, a Ph.D. in Organic Chemistry from the University of California, Los Angeles, and completed his training as a Howard Hughes Medical Institute post-doctoral fellow at Harvard University.

Deborah Morosini, M.D. has served as our Executive Vice President and Chief of Clinical Affairs since July 2020 and was an independent consultant to us and various other oncology companies from July 2019 to July 2020. Dr. Morosini previously served as Vice President of Clinical Affairs and Patient Engagement at Loxo Oncology, Inc., a biopharmaceutical company, from April 2016 to April 2019. Dr. Morosini served as Vice President of Clinical Affairs and Patient Engagement from August 2013 to April 2016 at Foundation Medicine, Inc., a molecular information company. Dr. Morosini received a B.A. degree in English from Mount Holyoke College, an M.S.W. degree from New York University's Graduate School of Social Work and an M.D. from Boston University School of Medicine.

Christopher Pierce, M.B.A. has served as our Executive Vice President and Chief of Business Operations since July 2020. Mr. Pierce previously served as Principal and Founder of Scout Advisers, LLC, a life sciences consultancy, from August 2019 to July 2020. Prior to that, Mr. Pierce served as Vice President, Head of Commercial from January 2018 to May 2019, and as Executive Director, Commercial from April 2017 to December 2017, at Loxo Oncology, Inc., a biopharmaceutical company. Mr. Pierce held several roles at Pfizer Inc., a biopharmaceutical company, including as Senior Director/Global Commercial Lead, Hematologic Malignancies Portfolio from July 2016 to March 2017, and as Portfolio Lead, US Marketing from March 2015 to July 2016. Mr. Pierce received an A.B. degree in Biochemical Sciences from Harvard College, and an M.B.A. from the Harvard Business School.

Non-Employee Directors

Paul A. Friedman, M.D. has served as a member of our board of directors since July 2016. Dr. Friedman has served as Chief Executive Officer and Chairman of the board of directors of Madrigal Pharmaceuticals, Inc., a biopharmaceutical company, since July 2016. Dr. Friedman previously served as the Chief Executive Officer of Incyte Corporation from November 2001 to January 2014. Dr. Friedman currently serves on the boards of directors of Incyte Corporation, Alexion Pharmaceuticals, Inc. and Madrigal Pharmaceuticals, Inc. He has previously served on the boards of directors of Cerulean Pharma Inc. and Verastem, Inc. Dr. Friedman received an A.B. in Biology from Princeton University and an M.D. from Harvard Medical School. We believe that Dr. Friedman's extensive experience in our business and on public company boards qualifies him to serve on our board of directors.

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David Bonita, M.D. has served as a member of our board of directors since July 2016. Dr. Bonita is a member of OrbiMed Advisors LLC, an investment firm. Dr. Bonita currently serves on the boards of directors of Acutus Medical, Inc., IMARA Inc., Repare Therapeutics Inc. and Tricida, Inc., as well as several private companies. Dr. Bonita also previously served on the boards of directors of Clementia Pharmaceuticals Inc., Loxo Oncology, Inc., SI-BONE, Inc., and ViewRay Inc. Prior to OrbiMed, Dr. Bonita worked as a corporate finance analyst in the healthcare investment banking groups of Morgan Stanley and UBS. He has published scientific articles in peer-reviewed journals based on signal transduction research performed at Harvard Medical School. He received a B.A. in biology from Harvard University and a joint M.D./M.B.A. from Columbia University. We believe that Dr. Bonita is qualified to serve on our board of directors based on his roles on several public and private boards of directors as well as his extensive experience in investing in healthcare companies.

Mardi C. Dier has served as a member of our board of directors since August 2020. Ms. Dier has served as Chief Financial Officer of Ultragenyx Pharmaceutical Inc. since October 2020. Ms. Dier previously served as Executive Vice President and Chief Financial Officer, and also as Chief Business Officer, of Portola Pharmaceuticals, Inc., a biopharmaceutical company, from November 2013 and October 2018, respectively, until its acquisition by Alexion Pharmaceuticals in July 2020, and as a Senior Vice President and Chief Financial Officer from August 2006 to November 2013. From 2003 to 2006, Ms. Dier served as Vice President of Investor Relations at Chiron Corporation, a biopharmaceutical company. From 1994 to 2001, Ms. Dier served as a Director, Investment Banking at Prudential Securities, Inc., a securities firm. Ms. Dier previously served as a supervising senior accountant at the audit department of KPMG Peat Marwick, an accounting firm, from 1986 to 1990. Ms. Dier currently serves as a director, and member of the audit committee, of Adamas Pharmaceuticals, Inc., a biopharmaceutical company, and as a director of ORIC Pharmaceuticals, Inc. Ms. Dier received a B.S. in Biology from Stanford University and an M.B.A. from the Anderson Graduate School of Management at the University of California, Los Angeles. We believe Ms. Dier is qualified to serve on our board of directors because of her experience in the biotechnology industry and her extensive experience in finance and accounting.

Kelvin Neu, M.D. is a Partner at Baker Bros. Advisors LP, a registered investment adviser. Since July 2019, Dr. Neu has served on the board of directors of IGM Biosciences, Inc., a biopharmaceutical company and is also on its research and clinical development committee. Since March 2020, Dr. Neu has served on the board of directors of Zymeworks, Inc., and is also on its research and development committee. Dr. Neu previously served on the board of directors of Idera Pharmaceuticals, Aquinox Pharmaceuticals and XOMA Corporation. Dr. Neu holds an M.D. from the Harvard Medical School-MIT Health Sciences and Technology program and spent three years in the Immunology Ph.D. program at Stanford University as a Howard Hughes Medical Institute Fellow. Dr. Neu holds an A.B. (summa cum laude) from Princeton University, where he was awarded the Khoury Prize for graduating first in his department of Molecular Biology. Prior to attending Princeton, Dr. Neu served for two and a half years in the military of his native Singapore. We believe Dr. Neu is qualified to serve on our board of directors because of his extensive investment and leadership experience, knowledge of our industry, and educational background in biology and biotechnology.

Victor Sandor, M.D.C.M. has served as a member of our board of directors since May 2020. From September 2014 to December 2019, Dr. Sandor served as the Chief Medical Officer at Array BioPharma Inc., a pharmaceutical company. From September 2014 to June 2019, he served as the Senior Vice President for Global Clinical Development at Incyte Corporation, a pharmaceutical company. From February 2010 to September 2014, Dr. Sandor served as the Vice President and Chief Medical Officer for oncology at Biogen Idec and, from October 2009 to February 2010, held positions of increasing responsibility in oncology product development at AstraZeneca. Dr. Sandor has served on the board of directors of ADC Therapeutics SA since April 2020 and Merus N.V. since June 2019. Dr. Sandor received a M.D.C.M. from McGill University in Montreal, Canada, and completed his Fellowship in Medical Oncology at the National Institutes of Health in Bethesda, Maryland. We believe that Dr. Sandor is qualified to serve on our board of directors due to his experience in the field of medicine, clinical drug development and scientific experience.

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Election of Officers

Our executive officers are appointed by, and serve at the discretion of, our board of directors. There are no family relationships among any of our directors or executive officers.

Board Composition

Our board of directors currently consists of six members. Five of our directors are independent within the meaning of the independent director guidelines of the Nasdaq Global Select Market, or Nasdaq. Each of our current directors will continue to serve until the election and qualification of his or her successor, or until his or her earlier death, resignation or removal.

Classified Board of Directors

In accordance with the terms of our restated certificate of incorporation and restated bylaws, our board of directors is divided into three staggered classes of directors. At each annual meeting of stockholders, a class of directors will be subject to re-election for a three-year term. As a result, only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Our directors is divided among the three classes as follows:

- the Class I directors are Paul A. Friedman and David Bonita and their terms will expire at the annual meeting of stockholders to be held in 2021;
- the Class II directors are Kelvin Neu and Victor Sandor and their terms will expire at the annual meeting of stockholders to be held in 2022; and
- the Class III directors are Kris Vaddi and Mardi C. Dier and their terms will expire at the annual meeting of stockholders to be held in 2023.

Each director's term continues until the election and qualification of his or her successor, or his or her earlier death, resignation or removal. Our restated certificate of incorporation and restated bylaws authorize only our board of directors to fill vacancies on our board of directors. Any increase or decrease in the number of directors will be distributed among the three classes so that, as nearly as possible, each class will consist of one-third of the directors. This classification of our board of directors may have the effect of delaying or preventing changes in control of our company. See the section entitled "Description of Capital Stock—Anti-Takeover Provisions—Restated Certificate of Incorporation and Restated Bylaw Provisions."

Director Independence

Our common stock is listed on Nasdaq. Under the rules of Nasdaq, independent directors must comprise a majority of a listed company's board of directors. In addition, the rules of Nasdaq require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating and governance committees be independent. Under the rules of Nasdaq, a director will only qualify as an "independent director" if, in the opinion of that company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director.

Audit committee members must also satisfy the independence criteria set forth in Rule 10A-3 under the Securities Exchange Act of 1934, as amended, or the Exchange Act. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors or any other board committee: (i) accept, directly or indirectly, any consulting, advisory or other compensatory fee from the listed company or any of its subsidiaries; or (ii) be an affiliated person of the listed company or any of its subsidiaries. We satisfy the audit committee independence requirements of Rule 10A-3. Additionally, compensation committee members must not have a relationship with us that is material to the director's ability to be independent from management in connection with the duties of a compensation committee member.

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Our board of directors has undertaken a review of the independence of each director and considered whether each director has a material relationship with us that could compromise his ability to exercise independent judgment in carrying out his responsibilities. As a result of this review, our board of directors determined that all of our directors, except for Kris Vaddi, are “independent directors” as defined under the applicable rules and regulations of the SEC and the listing requirements and rules of Nasdaq. In making these determinations, our board of directors reviewed and discussed information provided by the directors and us with regard to each director’s business and personal activities and relationships as they may relate to us and our management, including the beneficial ownership of our capital stock by each non-employee director and the transactions involving them described in the section entitled “Certain Relationships and Related Party Transactions.”

Committees of the Board of Directors

Our board of directors has an audit committee, a compensation committee and a nominating and governance committee, each of which, pursuant to its respective charter, has the composition and responsibilities described below. Copies of each charter are posted on the investor relations section of our website. Members serve on these committees until their resignation or until otherwise determined by our board of directors.

Audit Committee

Our audit committee is comprised of Mardi C. Dier, Paul A. Friedman and David Bonita, with Mardi C. Dier as the chairperson of our audit committee. Our board of directors has determined that the composition of our audit committee meets the requirements for independence under the current Nasdaq and SEC rules and regulations, and that each member of our audit committee is financially literate. In addition, our board of directors has determined that Mardi C. Dier is an “audit committee financial expert” as defined in Item 407(d)(5)(ii) of Regulation S-K promulgated under the Securities Act. This designation does not impose on her any duties, obligations or liabilities that are greater than are generally imposed on members of our audit committee and our board of directors. Our audit committee is directly responsible for, among other things:

- selecting and hiring our independent registered public accounting firm;
- the qualifications, independence and performance of our independent auditors;
- the preparation of the audit committee report to be included in our annual proxy statement;
- our compliance with legal and regulatory requirements;
- our accounting and financial reporting processes, including our financial statement audits and the integrity of our financial statements; and
- reviewing and approving related-person transactions.

Compensation Committee

Our compensation committee is comprised of David Bonita, Kelvin Neu and Mardi C. Dier, with David Bonita as the chairman of our compensation committee. Our board of directors has determined that each member of our compensation committee is a non-employee director, as defined by Rule 16b-3 promulgated under the Exchange Act, and meets the requirements for independence under the current Nasdaq listing standards and SEC rules and regulations. Our compensation committee is responsible for, among other things:

- evaluating, recommending, approving and reviewing executive officer compensation arrangements, plans, policies and programs;
- evaluating and recommending non-employee director compensation arrangements for determination by our board of directors;
- administering our cash-based and equity-based compensation plans; and

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- overseeing our compliance with regulatory requirements associated with the compensation of directors, officers and employees.

Nominating and Governance Committee

Our nominating and governance committee is comprised of Kelvin Neu, Victor Sandor and Paul Friedman, with Kelvin Neu as the chairman of our nominating and governance committee. Our board of directors has determined that each member of our nominating and governance committee meets the requirements for independence under the current Nasdaq listing standards. Our nominating and governance committee is responsible for, among other things:

- identifying, considering and recommending candidates for membership on our board of directors;
- overseeing the process of evaluating the performance of our board of directors; and
- advising our board of directors on other corporate governance matters.

Compensation Committee Interlocks and Insider Participation

None of the current members of our compensation committee has at any time been one of our officers or employees. None of our executive officers has served as a member of the board of directors, or as a member of the compensation or similar committee, of any entity that has one or more executive officers who served on our board of directors or compensation committee during the year ended December 31, 2019.

Prior to establishing the compensation committee in connection with our IPO, our full board of directors made decisions relating to the compensation of our officers.

Code of Business Conduct and Ethics

Our board of directors adopted a code of business conduct and ethics that applies to all of our employees, officers and directors, including our President and Chief Executive Officer and other executive and senior officers. The full text of our code of business conduct and ethics is posted on the investor relations section of our website. The reference to our website address in this prospectus does not include or incorporate by reference the information on our website into this prospectus. We intend to disclose future amendments to certain provisions of our code of business conduct and ethics, or waivers of these provisions, on our website or in public filings to the extent required by the applicable rules.

Non-Employee Director Compensation

During the year ended December 31, 2019, none of our non-employee directors received any fees or reimbursement of any expenses (other than customary expenses in connection with the attendance of meetings of our board of directors) or any equity or non-equity awards. Our Chief Executive Officer, Dr. Vaddi, received no compensation for his service as a director. Dr. Vaddi's compensation as a named executive officer is set forth below under "Executive Compensation—Summary Compensation Table."

Prior to the completion of our IPO, we did not have a formal policy to provide any cash or equity compensation to our non-employee directors for their service on our board of directors or committees of our board of directors.

Non-Employee Director Cash Compensation

Our non-employee directors receive an annual cash compensation of \$35,000 for service on the board, and additional cash compensation for the chairperson and committee members as set forth below. All cash payments are made quarterly in arrears, and pro-rated for any partial quarters of service.

- Chair of the Board: \$30,000

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- Audit Committee Chair (in lieu of membership fee): \$15,000
- Audit Committee Member (Non-Chair): \$7,500
- Compensation Committee Chair (in lieu of membership fee): \$10,000
- Compensation Committee Member (Non-Chair): \$5,000
- Nominating and Corporate Governance Committee Chair (in lieu of membership fee): \$8,000
- Nominating and Corporate Governance Committee Member (Non-Chair): \$4,000

Each non-employee director who is elected or appointed to our board of directors will be granted an option to purchase 46,688 shares of our common stock upon the director's initial appointment to our board of directors, referred to as an Initial Grant. The Initial Grant will vest in 36 annual installments on each monthly anniversary of the date of grant, such that the Initial Grant will become fully vested and exercisable on the third anniversary of the date of grant, subject to the directors continued service on each applicable vesting date or an earlier change of control of Prelude. If the non-employee director's service ends on the date of vesting, then the vesting will be deemed to have occurred.

In addition, each non-employee director who continues to serve on our board of directors following our annual meeting of stockholders will be granted an option to purchase 23,344 shares of our common stock on the date of such annual meeting of stockholders, referred to as an Annual Grant. Each Annual Grant will vest on the earlier of (a) the next annual meeting of the Company's stockholders and (b) the one-year anniversary of the grant date of the Annual Grant, subject to the director's continued service on the applicable vesting date or an earlier change in control of Prelude. If the non-employee director's service ends on the date of vesting, then the vesting will be deemed to have occurred.

In September 2020, our board of directors approved an option to purchase 46,688 shares of our common stock to each of Messrs. Friedman, Bonita and Neu and an option to purchase 43,230 shares of our common stock to Ms. Dier, in each case pursuant to the 2016 Plan and subject to the terms and conditions set forth in the applicable stock option agreements under such plan. In addition, each of Ms. Dier and Dr. Sandor each received an option to purchase 3,458 shares upon the effectiveness of our IPO registration statement pursuant to the 2020 Plan and subject to the terms and conditions set forth in the applicable stock option agreements under such plan, with an exercise per share of \$19.00.

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EXECUTIVE COMPENSATION

The following tables and accompanying narrative disclosure set forth information about the compensation earned by our named executive officers during the year ended December 31, 2019. Our named executive officers, who are our principal executive officer and the two most highly compensated executive officers (other than our principal executive officer) serving as executive officers as of December 31, 2019, were:

- Kris Vaddi, Ph.D., Chief Executive Officer;
- David Mauro, M.D., Ph.D., Chief Medical Officer; and
- Andrew P. Combs, Ph.D., Executive Vice President and Head of Chemistry.

Summary Compensation Table

The following table presents summary information regarding the total compensation for services rendered in all capacities that was awarded to and earned by our named executive officers during the year ended December 31, 2019.

<u>Name and Principal Position</u>	<u>Salary (\$)</u>	<u>Stock Awards \$(1)</u>	<u>Option Awards \$(1)</u>	<u>Non-Equity Incentive Plan Compensation \$(2)</u>	<u>Total (\$)</u>
Kris Vaddi, Ph.D.(3) <i>Chief Executive Officer</i>	315,000	815,000	828,125	121,275	2,079,400
David Mauro, M.D., Ph.D. <i>Chief Medical Officer</i>	250,000	—	437,500	96,731	784,231
Andrew P. Combs, Ph.D. <i>Executive Vice President and Head of Chemistry</i>	187,000	489,000	—	96,250	772,750

- (1) The amounts reported in the Stock Awards and Option Awards columns represent the aggregate grant date fair value of the awards granted under our 2016 Plan to the named executive officers during the year ended December 31, 2019 as computed in accordance with FASB ASC Topic 718, or ASC 718. The assumptions used in calculating the grant date fair value of the awards reported in the Stock Awards and Option Awards columns are set forth in Note 9 to our audited financial statements included elsewhere in this prospectus. Note that the amounts reported in this column reflect the aggregate accounting cost for these awards, and do not necessarily correspond to the actual economic value that may be received by the named executive officer from the awards.
- (2) For additional information regarding the non-equity incentive plan compensation, see “—Non-Equity Incentive Plan Awards.”
- (3) Dr. Vaddi is also a member of our board of directors but does not receive any additional compensation in his capacity as a director.

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Outstanding Equity Awards at 2019 Fiscal Year-End Table

The following table provides information regarding each unexercised stock option and share of restricted common stock held by our named executive officers as of December 31, 2019:

Name	Grant Date(1)	Option Awards				Stock Awards	
		Number of Securities Underlying Unexercised Options Exercisable	Number of Securities Underlying Unexercised Options Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares of Restricted Stock That Have Not Vested (#)	Market Value of Shares of Restricted Stock That Have Not Vested (\$)(2)
Kris Vaddi, Ph.D.	2/28/2017	12,969	—	0.31	2/27/2027	—	—
	6/17/2019	—	572,799(4)	1.89	6/16/2029	—	—
	10/5/2017	—	—	—	—	200,194(5)	377,418
	8/3/2018	—	—	—	—	227,323(5)	428,562
David Mauro, M.D., Ph.D.	6/17/2019	—	—	—	—	432,301(5)	815,000
	6/17/2019	—	302,611(4)	1.89	6/16/2029	—	—
Andrew P. Combs, Ph.D.	6/17/2019	—	—	—	—	259,380(5)	489,000

- (1) All outstanding equity awards were granted under the 2016 Plan.
- (2) There was no public market for our common stock as of December 31, 2019. The fair market value of our common stock as of December 31, 2019, as determined by an independent valuation, was \$1.89 per share.
- (3) This option was 100% vested on the grant date.
- (4) 1/4th of the option vests on the one-year anniversary of the vesting commencement date and an additional 1/48th vests monthly thereafter, subject to the executive's continued service to us. The options are also subject to acceleration of vesting upon a qualifying termination of employment, as described in greater detail in the "Employment Arrangements with our Named Executive Officers" section below.
- (5) The 1/4th of the restricted stock vests on the one-year anniversary of the vesting commencement date, and an additional 1/48th vests monthly thereafter for 36 months, subject to the executive's continued service to us. These shares would vest in full upon a qualifying termination of employment, as described in the "Employment Arrangements with our Named Executive Officers" section below.

Non-Equity Incentive Plan Awards

Annual bonuses for our executive officers are based on the achievement of corporate and, for all of the executive officers other than our Chief Executive Officer, individual performance objectives, as determined by our board of directors. For the 2019 bonuses, the corporate performance objectives included the IND submission of PRT811, advancing our product candidates in pre-clinical and clinical development and the establishment of development infrastructure capable of supporting advancement of the development candidates into the clinic. In March 2020, based on the achievement of these corporate performance objectives and satisfaction of individual performance goals, our board of directors determined to award bonuses equal to 110% of target.

Employment Arrangements with our Named Executive Officers

We have entered into written employment agreements with each of our named executive officers, setting forth the terms and conditions of employment of each named executive officer, including his initial base salary, target bonus, equity awards and employee benefit plan participation, including the following base salaries and target bonus opportunities for each of our named executive officers: Kris Vaddi: \$495,000 base salary and target bonus of 50% of base salary; David Mauro: \$404,300 base salary and target bonus of 40% of base salary; Andrew Combs: \$375,000 base salary and target bonus of 40% of base salary.

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Potential Payments upon Termination or Change in Control

Under the employment agreements with our named executive officers, in the event the named executive officer is terminated by the Company without “cause”, he will be entitled to receive his base salary and we will directly pay or reimburse the named executive officer for the cost of continued healthcare coverage, in each case for 12 months in the case of Dr. Vaddi and for nine months in the case of Dr. Mauro and Dr. Combs. In addition, Dr. Vaddi will be entitled to acceleration of his currently outstanding restricted shares.

In the event that the named executive officer is terminated without “cause” or he resigns for “good reason” within 12 months following a change in control of the company, in lieu of the foregoing, he will be entitled to receive (i) his base salary and we will directly pay or reimburse the named executive officer for the cost of continued healthcare coverage, in each case for 18 months in the case of Dr. Vaddi and for 12 months in the case of Dr. Mauro and Dr. Combs, (ii) a multiple of his annual target bonus opportunity equal to 150% for Dr. Vaddi and 100% for Dr. Mauro and Dr. Combs, and (iii) his equity awards will become fully vested and exercisable, as applicable.

The severance payments and benefits would be subject to the named executive officer’s execution of a general release of claims against us, and his agreement to comply with the non-competition and non-solicitation provisions in his proprietary information and restrictive covenant agreement. To the extent such severance payments and benefits are payable in connection with a change in control and would result in excise taxes imposed by Section 4999 of the Internal Revenue Code of 1986, as amended, then each of the named executive officers would be entitled to receive (i) the full payment of such payments and benefits or (ii) such lesser amount as would result in no portion of those payments and benefits being subject to the excise tax, whichever results in the greater net after-tax position for the executive.

Equity Plans

We believe that our ability to grant equity-based awards is a valuable compensation tool that enables us to attract, retain, and motivate our employees, consultants, and directors by aligning their financial interests with those of our stockholders. The principal features of our equity plans are summarized below. These summaries are qualified in their entirety by reference to the actual text of the plans, which are filed as exhibits to the registration statement of which this prospectus is a part.

2016 Stock Incentive Plan

Our 2016 Plan was initially adopted by our board of directors and approved by our stockholders in June 2016. The 2016 Plan has been amended from time to time, and was amended and restated in March 2020 to, among other things, expand the types of awards available for grant and make certain changes to the treatment of equity awards in connection with a change in control transaction. The 2016 Plan provides for the grant of options to purchase shares of our common stock, as well as for the award of restricted stock, or RSAs, restricted stock units, or RSUs, and stock appreciation rights, or SARs.

As of September 30, 2020, options to purchase 101,496 shares had been exercised and options to purchase 6,649,882 shares remained outstanding, with a weighted-average exercise price of \$7.00 per share. As of September 30, 2020, 2,260,562 shares of restricted stock were granted, of which all shares remained outstanding. No other types of awards have been granted under the 2016 Plan. The 2016 Plan terminated concurrently with the effectiveness of our 2020 Plan, and no additional grants were made pursuant to the 2016 Plan following its termination. However, any outstanding options and shares of restricted stock will remain outstanding until they are exercised, as applicable, or are terminated in accordance with the terms of the 2016 Plan and the applicable award agreements evidencing such awards.

Administration. Our 2016 Plan is administered by our compensation committee, referred to as the administrator. Subject to the terms of the 2016 Plan, the administrator has the authority to, among other things,

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select the persons to whom awards will be granted, construe and interpret our 2016 Plan as well as to prescribe, amend, expand, modify and rescind rules and regulations relating to the 2016 Plan.

Eligibility. Pursuant to the 2016 Plan, we may grant incentive stock options, which are intended to qualify for tax treatment as set forth under Section 422 of the Internal Revenue Code, as amended, or the Code, only to our employees (including officers and directors who are also employees). We may grant non-statutory stock options and all other types of awards to our employees (including officers and directors who are also employees), non-employee directors and consultants. We refer to employees, directors, or consultants who receive an award under our equity plans as participants.

Options. The 2016 Plan provides that the exercise price of each stock option must be at least equal to the fair market value of our common stock on the date of grant. However, the exercise price of any incentive stock option granted to a participant who owns more than ten percent of the total combined voting power of all classes of our capital stock, directly or by attribution, must be at least equal to 110% of the fair market value of our common stock on the date of grant.

The maximum permitted term of options granted under our 2016 Plan is ten years from the date of grant, except that the maximum permitted term of incentive stock options granted to a participant who owns more than ten percent of the total combined voting power of all classes of our capital stock, directly or by attribution, is five years from the date of grant.

Restricted Stock Awards. The 2016 Plan also provides for the issuance of RSAs pursuant to which the holder may purchase restricted shares of our common stock. Among other terms and conditions, we may retain an option to repurchase the unvested restricted stock at any time following the holder's termination of service.

Other Awards. The 2016 Plan was amended and restated in March 2020 to allow for the grant of RSUs and SARs, with terms as determined by our board of directors in accordance with the 2016 Plan. As of June 30, 2020, we have not granted any RSUs or SARs under the 2016 Plan.

Limited Transferability. Unless otherwise determined by the administrator, awards granted under our 2016 Plan generally may not be transferred or assigned in any manner other than by will or the laws of descent and distribution.

Change in Control. In the event of a "corporate transaction" (as defined in the 2016 Plan prior to its amendment and restatement), awards granted prior to the amendment and restatement of the 2016 Plan, may be (i) substituted or replaced by a successor entity with an equity award having substantially equivalent terms, or (ii) cancelled, provided that the administrator may provide for vested awards to be cancelled in exchange for payment equal to the value of shares underlying such awards (less any applicable exercise price), subject to certain notice requirements. The administrator may also elect to provide for partial or full accelerated vesting of such awards, or to change the terms of any award to reflect the corporate transaction, subject to certain limitations.

In the event of an "acquisition" or certain "other combinations" (each, as defined in the 2016 Plan), awards granted on or after the amendment and restatement of the 2016 Plan in March 2020 may be: (i) continued if we are the successor entity; (ii) assumed by the surviving corporation or its parent; (iii) substituted by the surviving corporation or its parent with new equity awards on substantially the same terms; (iv) cancelled for no consideration or in exchange for equivalent value in cash, cash equivalents, or securities of the successor entity, which payments may be deferred until the date or dates the award would have become exercisable or vested; (v) partially or fully accelerated; or (vi) any combination of the foregoing. Awards need not be treated identically.

Adjustments. In the event of a change in the number of outstanding shares of our common stock without consideration by reason of a stock dividend, recapitalization, stock split, reverse stock split, subdivision,

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combination, reclassification or other similar change in our capital structure, proportional adjustments may be made to the number of shares reserved for issuance under our 2016 Plan; the exercise prices, number and class of shares subject to outstanding options or SARs; the number and class of shares subject to other outstanding awards; and any applicable maximum award limits with respect to incentive stock options, in each case to prevent diminution or enlargement of the benefits or potential benefits intended to be made under the 2016 Plan.

Exchange, Repricing and Buyout of Awards. Pursuant to the 2016 Plan, as amended and restated, the administrator may, with the consent of the respective participants, issue new awards in exchange for the surrender and cancellation of any or all outstanding awards. Our board of directors may also reduce the exercise price of options or SARs or buy an award previously granted with payment in cash, shares or other consideration, in each case, subject to the terms of the 2016 Plan.

Amendment; Termination. The 2016 Plan terminated concurrently with the effectiveness of our 2020 Plan.

2020 Equity Incentive Plan

We have adopted our 2020 Equity Incentive Plan, or the 2020 Plan, which became effective on September 23, 2020, and it serves as the successor to our 2016 Plan. Our 2020 Plan authorizes the award of stock options, RSAs, SARs, RSUs, cash awards, performance awards and stock bonus awards. We have initially reserved 4,680,000 shares of our common stock, plus any reserved shares not issued or subject to outstanding grants under the 2016 Plan on the effective date of the 2020 Plan, for issuance pursuant to awards granted under our 2020 Plan. The number of shares reserved for issuance under our 2020 Plan will increase automatically on January 1 of each of 2021 through 2030 by the number of shares equal to the lesser of 5% of the aggregate number of outstanding shares of our common stock as of the immediately preceding December 31, or a number as may be determined by our board of directors.

In addition, the following shares will again be available for issuance pursuant to awards granted under our 2020 Plan:

- shares subject to options or SARs granted under our 2020 Plan that cease to be subject to the option or SAR for any reason other than exercise of the option or SAR;
- shares subject to awards granted under our 2020 Plan that are subsequently forfeited or repurchased by us at the original issue price;
- shares subject to awards granted under our 2020 Plan that otherwise terminate without such shares being issued;
- shares subject to awards granted under our 2020 Plan that are surrendered, cancelled or exchanged for cash or a different award (or combination thereof);
- shares issuable upon the exercise of options or subject to other awards granted under our 2016 Plan that cease to be subject to such options or other awards, by forfeiture or otherwise, after the termination of the 2016 Plan;
- shares of common stock subject to awards granted prior to the effectiveness of the 2016 Plan that are forfeited to or otherwise repurchased by us;
- shares subject to awards granted under our 2016 Plan that are forfeited or repurchased by us at the original price after the termination of the 2016 Plan; and
- shares subject to awards under our 2016 Plan or our 2020 Plan that are used to pay the exercise price of an option or withheld to satisfy the tax withholding obligations related to any award.

Administration. Our 2020 Plan is administered by our compensation committee, or by our board of directors acting in place of our compensation committee. Subject to the terms and conditions of the 2020 Plan, the

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administrator has the authority, among other things, to select the persons to whom awards may be granted, construe and interpret our 2020 Plan as well as to determine the terms of such awards and prescribe, amend and rescind the rules and regulations relating to the plan or any award granted thereunder. The 2020 Plan provides that the administrator may delegate its authority, including the authority to grant awards, to one or more executive officers to the extent permitted by applicable law, provided that awards granted to non-employee directors may only be determined by our board of directors.

Eligibility. Our 2020 Plan provides for the grant of awards to our employees, directors, consultants, independent contractors and advisors. No non-employee director may receive awards under our 2020 Plan that, when combined with cash compensation received as a non-employee director, exceed \$750,000 in a calendar year or \$1,000,000 in the calendar year of his or her initial services as a non-employee director with us.

Options. The 2020 Plan provides for the grant of both incentive stock options intended to qualify under Section 422 of the Code, and non-statutory stock options to purchase shares of our common stock at a stated exercise price. Incentive stock options may only be granted to employees, including officers and directors who are also employees. The exercise price of stock options granted under the 2020 Plan must be at least equal to the fair market value of our common stock on the date of grant. Incentive stock options granted to an individual who holds, directly or by attribution, more than ten percent of the total combined voting power of all classes of our capital stock must have an exercise price of at least 110% of the fair market value of our common stock on the date of grant. Subject to stock splits, dividends, recapitalizations or similar events, no more than 14,040,000 shares may be issued pursuant to the exercise of incentive stock options granted under the 2020 Plan.

Options may vest based on service or achievement of performance conditions. The administrator may provide for options to be exercised only as they vest or to be immediately exercisable, with any shares issued on exercise being subject to our right of repurchase that lapses as the shares vest. The maximum term of options granted under our 2020 Plan is ten years from the date of grant, except that the maximum permitted term of incentive stock options granted to an individual who holds, directly or by attribution, more than ten percent of the total combined voting power of all classes of our capital stock is five years from the date of grant.

Restricted Stock Awards. An RSA is an offer by us to sell shares of our common stock subject to restrictions, which may lapse based on the satisfaction of service or achievement of performance conditions. The price, if any, of an RSA will be determined by the compensation committee. Holders of RSAs, unlike holders of options, will have the right to vote and any dividends or stock distributions paid pursuant to RSAs will be accrued and paid when the restrictions on such shares lapse. Unless otherwise determined by the compensation committee at the time of award, vesting will cease on the date the participant no longer provides services to us and unvested shares may be forfeited to or repurchased by us.

Stock Appreciation Rights. A SAR provides for a payment, in cash or shares of our common stock (up to a specified maximum of shares, if determined by our compensation committee), to the holder based upon the difference between the fair market value of our common stock on the date of exercise and a predetermined exercise price, multiplied by the number of shares. The exercise price of a SAR must be at least the fair market value of a share of our common stock on the date of grant. SARs may vest based on service or achievement of performance conditions, and may not have a term that is longer than ten years from the date of grant.

Restricted Stock Units. RSUs represent the right to receive shares of our common stock at a specified date in the future, and may be subject to vesting based on service or achievement of performance conditions. Payment of earned RSUs will be made as soon as practicable on a date determined at the time of grant, and may be settled in cash, shares of our common stock or a combination of both. No RSU may have a term that is longer than ten years from the date of grant.

Performance Awards. Performance awards granted pursuant to the 2020 Plan may be in the form of a cash bonus, or an award of performance shares or performance units denominated in shares of our common stock

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that may be settled in cash, property or by issuance of those shares subject to the satisfaction or achievement of specified performance conditions.

Stock Bonus Awards. A stock bonus award provides for payment in the form of cash, shares of our common stock or a combination thereof, based on the fair market value of shares subject such award as determined by our compensation committee. The awards may be granted as consideration for services already rendered, or at the discretion of the compensation committee, may be subject to vesting restrictions based on continued service or performance conditions.

Cash Awards. A cash award is an award that is denominated in, or payable to an eligible participant solely in, cash.

Dividend Equivalent Rights. Dividend equivalent rights may be granted at the discretion of the administrator, and represent the right to receive the value of dividends, if any, paid by us in respect of the number of shares of our common stock underlying an award. Dividend equivalent rights will be subject to the same vesting or performance conditions as the underlying award and will be paid only at such time as the underlying award has become fully vested. Dividend equivalent rights may be settled in cash, shares or other property, or a combination of thereof as determined by the administrator.

Change of Control. Our 2020 Plan provides that, in the event of a “corporate transaction” (as defined in the 2020 Plan), awards granted under the 2020 Plan may (i) be continued by the company, if we are the successor entity; or (ii) assumed or substituted by the successor corporation, or a parent or subsidiary of the successor corporation, for substantially equivalent awards (including, but not limited to, an award to acquire the same consideration paid to our stockholders pursuant to the corporate transaction), in each case after taking into account appropriate adjustments for the number and kind of shares and exercise prices. The successor corporation may also issue, as replacement of our outstanding shares held by the participant, substantially similar shares, or other property subject to repurchase restrictions no less favorable to the participant. In the event the successor corporation refuses to assume, substitute, or replace any award, then such award will become fully vested and, as applicable, exercisable and any rights of repurchase or forfeiture restrictions thereon will lapse, immediately prior to the consummation of the corporation transaction. Awards with performance-based vesting criteria that are not assumed will be deemed earned and vested based on the greater of actual performance (if determinable) or 100% of target level, unless otherwise indicated pursuant to the terms and conditions of the applicable award agreement.

Adjustment. In the event of a change in the number of outstanding shares of our common stock without consideration by reason of a stock dividend, extraordinary dividend or distribution, recapitalization, stock split, reverse stock split, subdivision, combination, consolidation reclassification, spin-off or similar change in our capital structure, appropriate proportional adjustments may be made to the number of shares reserved for issuance under our 2020 Plan; the exercise prices, number and class of shares subject to outstanding options or SARs; the number and class of shares subject to other outstanding awards; and any applicable maximum award limits with respect to incentive stock options.

Exchange, Repricing and Buyout of Awards. The administrator may, with the consent of the respective participants, issue new awards in exchange for the surrender and cancellation of any or all outstanding awards.

The administrator may also reduce the exercise price of options or SARs or buy an award previously granted with payment in cash, shares or other consideration, in each case, subject to the terms of the 2020 Plan.

Clawback; Transferability. All awards will be subject to clawback or recoupment pursuant to any compensation clawback or recoupment policy adopted by our board of directors or required by law during the term of service of the award holder, to the extent set forth in such policy or applicable agreement. Except in limited circumstances, awards granted under our 2020 Plan may generally not be transferred in any manner prior to vesting other than by will or by the laws of descent and distribution.

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Amendment and Termination. Our board of directors may amend our 2020 Plan at any time, subject to stockholder approval as may be required. Our 2020 Plan will terminate ten years from the date our board of directors adopts the plan, unless it is terminated earlier by our board of directors. No termination or amendment of the 2020 Plan may adversely affect any then-outstanding award without the consent of the affected participant, except as is necessary to comply with applicable laws.

2020 Employee Stock Purchase Plan

We have adopted our 2020 Employee Stock Purchase Plan, or ESPP, which became effective on September 24, 2020 in order to enable eligible employees to purchase shares of our common stock with accumulated payroll deductions at a discount beginning on a date to be determined by our board of directors or our compensation committee. Our ESPP is intended to qualify under Section 423 of the Code.

Shares Available. We have initially reserved 520,000 shares of our common stock for sale under our ESPP. The aggregate number of shares reserved for sale under our ESPP will increase automatically on January 1st of each of the first ten calendar years after the first offering date by the number of shares equal to the lesser of 5% of the total outstanding shares of our common stock as of the immediately preceding December 31 (rounded to the nearest whole share) or a number of shares as may be determined by our board of directors in any particular year. The aggregate number of shares issued over the term of our ESPP, subject to stock-splits, recapitalizations or similar events, may not exceed 5,200,000 shares of our common stock.

Administration. Our ESPP is administered by our compensation committee, or by our board of directors acting in place of our compensation committee. Among other things, the administrator has the authority to determine eligibility for participation in the ESPP, designate separate offerings under the plan, and construe, interpret and apply the terms of the plan.

Eligibility. Employees eligible to participate in any offering pursuant to the ESPP generally include any employee that is employed by us or certain of our designated subsidiaries at the beginning of the offering period. However, our compensation committee may determine that employees who are customarily employed for 20 hours or less per week or for five months or less in a calendar year may not be eligible to participate in the ESPP. In addition, any employee who owns (or is deemed to own as a result of attribution) 5% or more of the total combined voting power or value of all classes of our capital stock, or the capital stock of one of our qualifying subsidiaries, or who will own such amount as a result of participation in the ESPP, will not be eligible to participate in the ESPP. The compensation committee may impose additional restrictions on eligibility from time to time.

Offerings. Under our ESPP, eligible employees will be offered the option to purchase shares of our common stock at a discount over a series of offering periods. Each offering period may itself consist of one or more purchase periods. No offering period may be longer than 27 months.

Participation. Participating employees will be able to purchase the offered shares of our common stock by accumulating funds through payroll deductions. Participants may select a rate of payroll deduction between 1% and 15% of their compensation. However, a participant may not purchase more than 2,500 shares during any one purchase period, and may not subscribe for more than \$25,000 in fair market value of shares of our common stock (determined as of the date the offering period commences) in any calendar year in which the offering is in effect. The administrator, in its discretion, may set a lower maximum amount of shares which may be purchased.

The purchase price for shares of our common stock purchased under the ESPP will be 85% of the lesser of the fair market value of our common stock on (i) the first trading day of the applicable offering period or (ii) the last trading day of each purchase period in the applicable offering period.

Once an employee becomes a participant in an offering period, the participant will be automatically enrolled in each subsequent offering period at the same contribution level. A participant may reduce his or her

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contribution in accordance with procedures set forth by the compensation committee and may withdraw from participation in the ESPP at any time prior the end of an offering period, or such other time as may be specified by the compensation committee. Upon withdrawal, the accumulated payroll deductions will be returned to the participant without interest.

Adjustments upon Recapitalization. If the number of outstanding shares of our common stock is changed by stock dividend, recapitalization, stock split, reverse stock split, subdivision, combination, reclassification or similar change in our capital structure without consideration, then our compensation committee will proportionately adjust the number and class of common stock that is available under the ESPP, the purchase price and number of shares any participant has elected to purchase as well as the maximum number of shares which may be purchased by participants.

Change of Control. If we experience a change of control transaction, any offering period that commenced prior to the closing of the proposed change of control transaction will be shortened and terminated on a new purchase date. The new purchase date will occur on or prior to the closing of the proposed change of control transaction, and our ESPP will then terminate on the closing of the proposed change of control.

Transferability. A participant may not assign, transfer, pledge or otherwise dispose of payroll deductions credited to his or her account, or any rights with regard to an election to purchase shares pursuant to the ESPP other than by will or the laws of descent or distribution.

Amendment; Termination. The administrator may amend, suspend or terminate the ESPP at any time without stockholder consent, except as required by law. Our ESPP will continue until the earlier to occur of (a) termination of the ESPP by our board of directors, (b) issuance of all of the shares reserved for issuance under the ESPP, or (c) the tenth anniversary of the effective date under the ESPP.

401(k) Plan

We sponsor a retirement savings plan that is intended to qualify for favorable tax treatment under Section 401(a) of the Code and contains a cash or deferred feature that is intended to meet the requirements of Section 401(k) of the Code. Participants may make pre-tax and certain after-tax (Roth) salary deferral contributions to the plan from their eligible earnings up to the statutorily prescribed annual limit under the Code. Participants who are 50 years of age or older may contribute additional amounts based on the statutory limits for catch-up contributions. Participant contributions are held in trust as required by law. We expect to make discretionary matching contributions beginning January 1, 2021, which contributions will be subject to vesting conditions.

Other Benefits

Our named executive officers are eligible to participate in our employee benefit plans on the same basis as our other employees, including our 401(k) plan, and health and welfare plans.

Limitations on Liability and Indemnification Matters

Our restated certificate of incorporation contains provisions that limit the liability of our directors for monetary damages to the fullest extent permitted by the Delaware General Corporation Law, or DGCL. Consequently, our directors will not be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duties as directors, except liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;

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- unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the DGCL; or
- any transaction from which the director derived an improper personal benefit.

Our restated certificate of incorporation and our restated bylaws require us to indemnify our directors and officers to the maximum extent not prohibited by the DGCL and allow us to indemnify other employees and agents as set forth in the DGCL.

We have entered, and intend to continue to enter, into separate indemnification agreements with our directors, officers and certain of our key employees, in addition to the indemnification provided for in our restated certificate of incorporation and restated bylaws. These agreements, among other things, require us to indemnify our directors, officers and key employees for certain expenses, including attorneys' fees, judgments, penalties, fines and settlement amounts actually incurred by these individuals in any action or proceeding arising out of their service to us or any of our subsidiaries or any other company or enterprise to which these individuals provide services at our request. Subject to certain limitations, our indemnification agreements also require us to advance expenses incurred by our directors, officers and key employees for the defense of any action for which indemnification is required or permitted.

We believe that these indemnification provisions and agreements are necessary to attract and retain qualified directors, officers and key employees. We also maintain directors' and officers' liability insurance.

The limitation of liability and indemnification provisions in our restated certificate of incorporation and restated bylaws may discourage stockholders from bringing a lawsuit against our directors and officers for breach of their fiduciary duty. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and other stockholders. Further, a stockholder's investment may be adversely affected to the extent that we pay the costs of settlement and damage awards against directors and officers as required by these indemnification provisions.

At present, there is no pending litigation or proceeding involving any of our directors or executive officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, executive officers or persons controlling us, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

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CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

In addition to the compensation arrangements, including employment, termination of employment and change in control arrangements, with our directors and executive officers, including those discussed in the sections entitled “Management” and “Executive Compensation,” the following is a description of each transaction since January 1, 2017 and each currently proposed transaction in which:

- we have been or are to be a participant;
- the amounts involved exceeded or will exceed the lesser of \$120,000 and 1% of our total assets; and
- any of our directors, executive officers or holders of more than 5% of our capital stock, or an affiliate or immediate family member of the foregoing persons, had or will have a direct or indirect material interest.

Other than as described below, there have not been, nor are there any currently proposed, transactions or series of similar transactions to which we have been or will be a party other than compensation arrangements, which are described where required under the section entitled “Executive Compensation.”

Series A Convertible Preferred Stock Financing

In two closings in October 2017 and August 2018, we sold an aggregate of 9,499,556 shares of our Series A convertible preferred stock at a purchase price of \$3.1423 per share for an aggregate purchase price of approximately \$30.0 million. In addition, holders of our then-outstanding preferred stock prior to the Series A convertible preferred stock financing, such preferred stock referred to as the 2016 Preferred Stock, converted their shares of 2016 Preferred Stock to an aggregate of 2,236,563 shares of our Series A convertible preferred stock. Each share of our Series A convertible preferred stock converted automatically into one share of our common stock or our non-voting common stock, as applicable, upon our IPO in September 2020.

The purchasers of our Series A convertible preferred stock are entitled to specified registration rights. For additional information, see “Description of Capital Stock—Registration Rights.” The following table summarizes the Series A convertible preferred stock purchased by members of our board of directors or their affiliates and holders of more than 5% of our outstanding capital stock. The terms of these purchases were the same for all purchasers of our Series A convertible preferred stock. Please refer to the section titled “Principal Stockholders” for more details regarding the shares held by these entities.

<u>Name of Stockholder</u>	<u>Purchased Shares of Series A Convertible Preferred Stock</u>	<u>Total Purchase Price (\$)</u>	<u>Converted Shares of Series A Convertible Preferred Stock</u>	<u>Total Shares of Series A Convertible Preferred Stock</u>
Entities affiliated with Baker Brothers	4,614,526 ⁽¹⁾	14,500,001	876,709 ⁽²⁾	5,491,235
Paul A. Friedman ⁽³⁾	79,560	249,999	216,234	295,794
OrbiMed Private Investments VI, LP ⁽⁴⁾	4,614,526	14,500,001	876,711	5,491,237

(1) Consists of 4,153,065 shares of Series A Preferred Stock purchased by Baker Brothers Life Sciences L.P., or Life Sciences, and 461,461 shares of Series A Preferred Stock purchased by 667, L.P., or 667, and together with Life Sciences, the Baker Funds. The Baker Funds collectively hold more than 5% of our outstanding capital stock. Baker Bros. Advisors LP, or the Adviser, is the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over investments. Kelvin Neu, a member of our board of directors, is an employee of the Adviser, but does not have any right to the securities held by the Baker Funds.

(2) Consists of 789,039 shares of Series A Preferred Stock converted from 2016 Preferred Stock and held by Life Sciences and 87,670 shares of Series A Preferred Stock converted from 2016 Preferred Stock and held

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by 667. The Baker Funds collectively hold more than 5% of our outstanding capital stock. The Adviser is the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over investments. Kelvin Neu, a member of our board of directors, is an employee of the Adviser but does not have any right to the securities held by the Baker Funds.

- (3) Paul A. Friedman is a member of our board of directors.
- (4) OrbiMed Private Investments VI, LP, or OPI VI, holds more than 5% of our outstanding capital stock. OrbiMed Capital GP VI LLC, or OrbiMed GP VI, is the general partner of OPI VI and OrbiMed Advisors LLC, or OrbiMed Advisors, a registered investment adviser under the Investment Advisors Act of 1940, as amended, is the managing member of OrbiMed GP VI. David A. Bonita, a member of our board of directors, is a member of OrbiMed Advisors.

Series B Convertible Preferred Stock Financing

In two closings in May 2019 and March 2020, we sold an aggregate of 15,257,692 shares of our Series B convertible preferred stock at a purchase price of \$3.9325 per share for an aggregate purchase price of approximately \$60.0 million. Each share of our Series B convertible preferred stock converted automatically into one share of our common stock or our non-voting common stock, as applicable, upon our IPO in September 2020.

The purchasers of our Series B convertible preferred stock are entitled to specified registration rights. For additional information, see “Description of Capital Stock—Registration Rights.” The following table summarizes the Series B convertible preferred stock purchased by members of our board of directors or their affiliates and holders of more than 5% of our outstanding capital stock. The terms of these purchases were the same for all purchasers of our Series B convertible preferred stock. Please refer to the section titled “Principal Stockholders” for more details regarding the shares held by these entities.

<u>Name of Stockholder</u>	<u>Shares of Series B Convertible Preferred Stock</u>	<u>Total Purchase Price (\$)</u>
Entities affiliated with Baker Brothers ⁽¹⁾	7,363,644	28,957,093
Paul A. Friedman ⁽²⁾	152,576	599,998
OrbiMed Private Investments VI, LP ⁽³⁾	7,363,644	28,957,093

- (1) Consists of 6,746,058 shares of Series B Preferred Stock purchased by Life Sciences and 617,586 shares of Series B Preferred Stock purchased by 667. The Baker Funds collectively hold more than 5% of our outstanding capital stock. The Adviser is the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over investments. Kelvin Neu, a member of our board of directors, is an employee of the Adviser but does not have any right to the securities held by the Baker Funds.
- (2) Paul A. Friedman is a member of our board of directors.
- (3) OPI VI holds more than 5% of our outstanding capital stock. OrbiMed GP VI is the general partner of OPI VI and OrbiMed Advisors is the managing member of OrbiMed GP VI. David A. Bonita, a member of our board of directors, is a member of OrbiMed Advisors.

Series C Convertible Preferred Stock Financing

In August 2020, we sold an aggregate of 3,443,612 shares of our Series C convertible preferred stock at a purchase price of \$14.5197 per share for an aggregate purchase price of approximately \$50.0 million. Each share of our Series C convertible preferred stock converted automatically into one share of our common stock or our non-voting common stock, as applicable, upon our IPO in September 2020.

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The purchasers of our Series C convertible preferred stock are entitled to specified registration rights. For additional information, see “Description of Capital Stock—Registration Rights.” The following table summarizes the Series C convertible preferred stock purchased by members of our board of directors or their affiliates and holders of more than 5% of our outstanding capital stock. The terms of these purchases were the same for all purchasers of our Series C convertible preferred stock. Please refer to the section titled “Principal Stockholders” for more details regarding the shares held by these entities.

<u>Name of Stockholder</u>	<u>Shares of Series C Convertible Preferred Stock</u>	<u>Total Purchase Price (\$)</u>
Entities affiliated with Baker Brothers ⁽¹⁾	1,033,084	14,999,989
OrbiMed Private Investments VI, LP ⁽²⁾	1,033,084	14,999,989

- (1) Consists of 957,211 shares of Series C Preferred Stock purchased by Life Sciences and 75,873 shares of Series C Preferred Stock purchased by 667. The Baker Funds collectively hold more than 5% of our outstanding capital stock. The Adviser is the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over investments. Kelvin Neu, a member of our board of directors, is an employee of the Adviser but does not have any right to the securities held by the Baker Funds.
- (2) OPI VI holds more than 5% of our outstanding capital stock. OrbiMed GP VI is the general partner of OPI VI and OrbiMed Advisors is the managing member of OrbiMed GP VI. David A. Bonita, a member of our board of directors, is a member of OrbiMed Advisors.

Investors’ Rights Agreement

We have entered into an investors’ rights agreement, or the IRA, dated August 21, 2020 with certain holders of our then outstanding convertible preferred stock, including entities with which certain of our executive officers and directors are affiliated. These stockholders are entitled to rights with respect to the registration of their shares under the Securities Act. For a description of these registration rights, see the section entitled “Description of Capital Stock—Registration Rights.”

Participation in Our Initial Public Offering

OrbiMed Private Investments VI, LP and its affiliated entities, and the Baker Funds, each a holder of more than 5% of our common stock and an affiliate of a member of our board of directors, and certain of our executive officers, each purchased, through their affiliated entities, 3,094,141 shares of our common stock in our initial public offering at the initial public offering price.

Registration Rights Agreement

Pursuant to the right each party had under the IRA, we have entered into a registration rights agreement, or the Post-IPO RRA, each dated December 20, 2020 with each of Baker Brothers and its affiliates, OrbiMed and its affiliates and Kris Vaddi, or collectively, the RRA Investors. Pursuant to the Post-IPO RRA, the RRA Investors are entitled to rights with respect to the registration of their shares under the Securities Act that supersede such rights held by the RRA Investors under the IRA. For a description of these registration rights, see the section entitled “Description of Capital Stock—Registration Rights—Registration Rights Agreement.”

Equity Grants to Executive Officers and Directors

We have granted stock options to our executive officers and certain directors, as more fully described in the sections entitled “Executive Compensation” and “Management—Non-Employee Director Compensation,” respectively.

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Director and Executive Officer Compensation

Please see the sections entitled “Management—Non-Employee Director Compensation” and “Executive Compensation” for information regarding the compensation of our directors and executive officers.

Employment Agreements

We have entered into employment agreements with certain of our executive officers. For more information regarding these agreements, see the section entitled “Executive Compensation—Employment Arrangements with our Named Executive Officers.”

Indemnification Agreements

We have entered into new indemnification agreements with each of our directors and executive officers. The indemnification agreements, our restated certificate of incorporation and our restated bylaws will require us to indemnify our directors to the fullest extent not prohibited by Delaware law. Subject to certain limitations, our restated bylaws also require us to advance expenses incurred by our directors and officers. For more information regarding these agreements, see the section entitled “Executive Compensation—Limitations on Liability and Indemnification Matters” for information on our indemnification arrangements with our directors and executive officers.

Policies and Procedures for Related Party Transactions

We have adopted a written related person transactions policy that provides that our executive officers, directors, nominees for election as a director, beneficial owners of more than 5% of our common stock, and any members of the immediate family of and any entity affiliated with any of the foregoing persons, are not permitted to enter into a material related person transaction with us without the review and approval of our audit committee, or a committee composed solely of independent directors in the event it is inappropriate for our audit committee to review such transaction due to a conflict of interest. Under the policy, any request for us to enter into a transaction with an executive officer, director, nominee for election as a director, beneficial owner of more than 5% of our common stock or with any of their immediate family members or affiliates in which the amount involved exceeds \$120,000 will be presented to our audit committee (or the committee composed solely of independent directors, if applicable) for review, consideration and approval. In approving or rejecting any such proposal, our audit committee (or the committee composed solely of independent directors, if applicable) will consider the relevant facts and circumstances available and deemed relevant to the audit committee (or the committee composed solely of independent directors, if applicable), including, but not limited to, whether the transaction is on terms no less favorable than terms generally available to an unaffiliated third party under the same or similar circumstances and the extent of the related person’s interest in the transaction.

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PRINCIPAL STOCKHOLDERS

The following table and accompanying footnotes set forth certain information with respect to the beneficial ownership of our common stock and non-voting common stock at November 30, 2020, and as adjusted to reflect the shares of common stock to be issued and sold in this offering, for:

- each of our directors;
- each of our named executive officers;
- all of our current directors and executive officers as a group; and
- each person, or group of affiliated persons, who beneficially owned more than 5% of our outstanding shares of common stock and non-voting common stock.

We have determined beneficial ownership in accordance with the rules of the SEC, and the information is not necessarily indicative of beneficial ownership for any other purpose. Except as indicated by the footnotes below, we believe, based on information furnished to us, that the persons and entities named in the table below have sole voting and sole investment power with respect to all shares of common stock that they beneficially owned, subject to applicable community property laws.

Beneficial ownership prior to this offering is based on 43,703,381 shares of common stock outstanding as of November 30, 2020 (of which 11,110,371 shares are non-voting common stock). Beneficial ownership after this offering is based on _____ shares of common stock outstanding, assuming the issuance of _____ shares of common stock in this offering, which does not contemplate exercise of the underwriters' option to purchase additional shares.

In computing the number of shares of common stock beneficially owned by a person and the percentage ownership of that person, we deemed to be outstanding all shares of common stock subject to options held by that person or entity that are currently exercisable or that will become exercisable within 60 days of November 30, 2020, although these shares are not considered outstanding for purposes of computing the percentage ownerships of any other person. We did not deem these shares outstanding, however, for the purpose of computing the percentage ownership of any other person. Unless otherwise indicated, the address of each beneficial owner listed in the table below is c/o Prelude Therapeutics Incorporated, 200 Powder Mill Road, Wilmington, DE 19803.

Name of Beneficial Owner	Number of Shares Beneficially Owned		Percentage of Shares Beneficially Owned			
	Voting Common Stock	Non-Voting Common Stock	Voting Common Stock		Non-Voting Common Stock	
			Prior to this Offering	After this Offering	Prior to this Offering	After this Offering
Directors and Named Executive Officers:						
Kris Vaddi ⁽¹⁾	2,913,906	—	8.9%		—	
David Mauro ⁽²⁾	126,087	—	*		—	
Andrew P. Combs ⁽³⁾	260,380	—	*		—	
Paul A. Friedman	505,286	—	1.6		—	
David Bonita ⁽⁴⁾	10,044,879	5,555,186	30.8		50.0%	
Mardi C. Dier ⁽⁵⁾	16,388	—	*		—	
Kelvin Neu ⁽⁶⁾	5,188	—	*		—	
Victor Sandor ⁽⁷⁾	384	—	*		—	
All executive officers and directors as a group (12 persons)	14,239,827	5,555,186	42.9		50.0	
Other 5% or Greater Stockholders:						
OrbiMed Entities ⁽⁸⁾	10,039,691	5,555,186	30.8		50.0	
Baker Brothers Entities ⁽⁹⁾	10,123,824	5,555,185	31.1		50.0	

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- * Represents beneficial ownership of less than one percent.
- (1) Represents (i) 2,913,906 shares of common stock held by Dr. Vaddi, of which (a) 951,786 shares are unvested and subject to forfeiture to us if Dr. Vaddi ceases to provide service to us prior to the vesting of the shares and (b) 239,705 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020, (ii) 101,477 shares of common stock held by Sidus Ventures, LLC and (iii) 423,655 shares of common stock held by Dolphin City Trust. Dr. Vaddi is the manager of Sidus Ventures, LLC and may be deemed to have beneficial ownership over the securities held by Sidus Ventures, LLC. Dr. Vaddi is the beneficiary of Dolphin City Trust and may be deemed to have beneficial ownership over the securities held by Dolphin City Trust.
 - (2) Represents 126,087 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020.
 - (3) Represents 260,380 shares of common stock, of which 156,710 shares are unvested and subject to forfeiture to us if Dr. Combs ceases to provide service to us prior to the vesting of the shares.
 - (4) Represents (i) shares of common stock referenced in footnote (8) below and (ii) 5,188 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020. For the common stock referenced in footnote (8) below, Dr. Bonita is a member of OrbiMed Advisors, but he disclaims beneficial ownership of the shares held by OPI VI, except to the extent of his pecuniary interest therein if any.
 - (5) Represents 16,388 shares of common stock, of which 6,388 shares of common stock are subject to options that are exercisable within 60 days of November 30, 2020.
 - (6) Represents 5,188 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020.
 - (7) Represents 384 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020.
 - (8) Based solely on information contained in a Schedule 13D filed with the SEC on October 5, 2020 by OrbiMed Advisors LLC, or OrbiMed Advisors, and related entities. Represents (i) 9,250,191 shares of our common stock and 5,555,186 shares of our non-voting common stock held by OrbiMed Private Investments VI, LP, or OPI VI, (ii) 263,200 shares of our common stock held by The Biotech Growth Trust PLC and (iii) 526,300 shares of our common stock held by OrbiMed Partners Master Fund Limited. OrbiMed Capital GP VI LLC, or OrbiMed GP VI, is the general partner of OPI VI and OrbiMed Advisors, a registered investment adviser under the Investment Advisors Act of 1940, as amended, is the managing member of OrbiMed GP VI. By virtue of such relationships, OrbiMed GP VI and OrbiMed Advisors may be deemed to have voting and investment power over the securities held by OPI VI and as a result may be deemed to have beneficial ownership over such securities. David Bonita, a member of OrbiMed Advisors, is a member of our board of directors. Each of OrbiMed GP VII, OrbiMed Advisors, and David Bonita disclaims beneficial ownership of the shares held by OPI VI, except to the extent of its or his pecuniary interest therein if any. OrbiMed Capital LLC, or OrbiMed Capital, is the portfolio manager to The Biotech Growth Trust PLC and the investment advisor to OrbiMed Partners Master Fund Limited. By virtue of such relationships, OrbiMed Capital may be deemed to have voting and investment power over the securities held by The Biotech Growth Trust PLC and OrbiMed Partners Master Fund Limited, and as a result may be deemed to have beneficial ownership over such securities. OrbiMed Capital is a relying advisor of OrbiMed Advisors. OrbiMed Capital and OrbiMed Advisors exercise voting and investment power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein. The address of the OrbiMed Entities is 601 Lexington Avenue, 54th Floor, New York, NY 10022.
 - (9) Based solely on information contained in a Schedule 13D filed with the SEC on September 30, 2020 by Baker Bros. Advisors LP, or the Adviser, and related entities. Represents (i) 870,873 shares of our common stock and 497,036 shares of our non-voting common stock held by 667, L.P., or 667, (ii) 9,247,763 shares of our common stock and 5,058,149 shares of our non-voting common stock held by Baker Brothers Life Sciences, L.P., or Life Sciences and together with 667, the Baker Funds, and (iii) 5,188 shares of common stock subject to options that are exercisable within 60 days of November 30, 2020, held by Dr. Neu, a member of our board of directors. The Adviser is the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over

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investments. Baker Bros. Advisors (GP) LLC, or the Adviser GP is the sole general partner of the Adviser. Julian C. Baker and Felix J. Baker are the managing members of the Adviser GP. Dr. Neu, an employee of the Advisor and a member of our board of directors, does not have any right to the securities held by the Baker Funds. The Advisor GP, Felix J. Baker and Julian C. Baker as managing members of the Adviser GP, and the Adviser may be deemed to be beneficial owners of the common shares directly held by the Baker Funds. Julian C. Baker and Felix J. Baker disclaim beneficial ownership of these securities, except to the extent of their pecuniary interest therein. The address for the Adviser, the Adviser GP, Felix J. Baker and Julian C. Baker is c/o Baker Bros. Advisors LP, 860 Washington Street, 3rd Floor, New York, NY 10014.

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DESCRIPTION OF CAPITAL STOCK

The following description summarizes the most important terms of our capital stock, our restated certificate of incorporation and our restated bylaws. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description, you should refer to our restated certificate of incorporation and restated bylaws, which are included as exhibits to the registration statement of which this prospectus forms a part, and to the applicable provisions of Delaware law.

General

Our authorized capital stock consists of 487,149,741 shares of common stock, \$0.0001 par value per share, 12,850,259 shares of non-voting common stock, \$0.0001 par value per share, and 10,000,000 shares of undesignated preferred stock, \$0.0001 par value per share. Our board of directors is authorized, without stockholder approval, to issue additional shares of our capital stock.

Common Stock and Non-Voting Common Stock

Holders of our common stock have no conversion rights, while holders of our non-voting common stock have the right to convert each share of our non-voting common stock into one share of common stock at such holder's election, provided that as a result of such conversion, such holder, together with its affiliates and any members of a Schedule 13(d) group with such holder, would not beneficially own in excess of 9.99% of our common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in our restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder of non-voting common stock upon 61 days' notice to us.

Dividend Rights

Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of our common stock and our non-voting common stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine. See the section entitled "Dividend Policy."

Voting Rights

Except as otherwise expressly provided in our restated certificate of incorporation or as required by applicable law, on any matter that is submitted to a vote by our stockholders, holders of our common stock are entitled to one vote per share of common stock, and holders of our non-voting common stock are not entitled to any votes per share of non-voting common stock, including for the election of directors. We have not provided for cumulative voting for the election of directors in our restated certificate of incorporation, which means that holders of a majority of the shares of our common stock are able to elect all of our directors. Our restated certificate of incorporation established a classified board of directors, to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No Preemptive or Similar Rights

Neither our common stock nor our non-voting common stock is entitled to preemptive rights, and neither is subject to conversion, redemption or sinking fund provisions.

Right to Receive Liquidation Distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock and our non-voting common

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stock and any participating preferred stock outstanding at that time, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights of and the payment of liquidation preferences, if any, on any outstanding shares of preferred stock.

Preferred Stock

We had no shares of preferred stock outstanding as of September 30, 2020.

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders. Our board of directors is also able to increase or decrease the number of shares of any series of preferred stock, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock. We have no current plan to issue any shares of preferred stock.

Stock Options

As of September 30, 2020, we had outstanding options to purchase an aggregate 6,649,882 shares of our common stock, with a weighted average exercise price of \$7.00.

Registration Rights

As of September 30, 2020, the holders of 30,437,423 shares of our common stock and non-voting common stock are entitled to rights with respect to the registration of these shares (or, in the case of the non-voting common stock, the shares of common stock into which such shares are convertible) under the Securities Act as described below. We refer to these shares collectively as registrable securities. These rights are provided under the terms of the IRA between us and the holders of these shares, which was entered into in connection with our redeemable convertible preferred stock financings prior to our IPO and under the terms of the Post-IPO RRA between us and the RRA Investors.

Demand Registration Rights

Beginning from March 23, 2021, if the holders of not less than 50% of the then-outstanding registrable securities may request the registration under the Securities Act of any registrable securities, if the anticipated aggregate offering price, net of selling expenses, would exceed \$10.0 million, we are obligated to provide notice of such request to all holders of registration rights and, as soon as practicable and in any event within 60 days, file a Form S-1 registration statement under the Securities Act covering all registrable securities that the initiating holders requested to be registered and any additional registrable securities requested to be included in such registration by any other holders. We are only required to file two registration statements that are declared effective upon exercise of these demand registration rights. We may postpone taking action with respect to such filing not more than once during any 12-month period for a period of not more than 90 days, if after receiving a request for registration, we furnish to the holders requesting such registration a certificate signed by our Chief Executive Officer stating that, in the good faith judgment of our board of directors, it would be materially detrimental to us and our stockholders; provided that we may not register any securities for our own account or that of any other stockholder during such 90-day period other than under certain circumstances.

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Form S-3 Registration Rights

The holders of at least 25% of the then-outstanding registrable securities can request that we register all or part of their shares on Form S-3 if we are eligible to file a registration statement on Form S-3 and if the aggregate price to the public of the shares offered, net of selling expenses, is at least \$5.0 million. The stockholders may only require us to effect two registration statements on Form S-3 in a 12-month period. We may postpone taking action with respect to such filing not more than once during any 12-month period for a period of not more than 90 days, if after receiving a request for registration, we furnish to the holders requesting such registration a certificate signed by our Chief Executive Officer stating that, in the good faith judgment of our board of directors, it would be materially detrimental to us and our stockholders; provided that we may not register any securities for our own account or that of any other stockholder during such 90-day period other than under certain circumstances.

Piggyback Registration Rights

If we register any of our securities for public sale in cash, holders of then-outstanding registrable securities or their permitted transferees will have the right to include their registrable securities in the registration statement. However, this right does not apply to a registration relating to any of our employee benefit plans, a corporate reorganization or transaction under Rule 145 of the Securities Act, a registration that requires information that is not substantially the same as the information required to be included in a registration statement covering the sale of the registrable securities, or a registration in which the only common stock being registered is common stock issuable upon conversion of debt securities that are also being registered or issuable upon the exercise of warrants. In an underwritten offering, if the total number of securities requested by stockholders to be included in the offering exceeds the number of securities to be sold (other than by us) that the underwriters determine in their reasonable discretion is compatible with the success of the offering, then we will be required to include only that number of securities that the underwriters and us, in our sole discretion, determine will not jeopardize the success of the offering. If the underwriters determine that less than all the registrable securities requested to be registered can be included in the offering, the number of registrable shares to be registered will be allocated (i) first, among holders of our preferred stock, in proportion to the amount of common stock issued or issuable upon conversion of the preferred stock owned by each such holder to be included in such offering, and (ii) second, among all other holders of our registrable securities, in proportion to the amount of other registrable securities owned by each such holder. However, (i) the number of shares issued or issuable upon conversion of the preferred stock, to be registered by the holders of our preferred stock, cannot be reduced unless all other securities (other than as offered by us) are first excluded entirely, and (ii) the number of shares to be registered by holders of all other registrable securities cannot be reduced unless all other securities (other than as offered by us and the shares of common stock issued or issuable on conversion of our preferred stock) are first entirely excluded. The number of registrable securities included in the offering may not be reduced below 25% of the total number of securities included in such offering, except for in connection with an initial public offering, in which case the underwriters may exclude these holders entirely.

Expenses of Registration Rights

We generally will pay all expenses, other than underwriting discounts and selling commissions incurred in connection with each of the registrations described above, including the reasonable fees and disbursements, not to exceed \$15,000, of one counsel for the selling holders.

Expiration of Registration Rights

The registration rights described above will expire, with respect to any particular holder of these rights, on the earliest to occur of (a) at such time that all of the holder's registrable securities can be sold without limitation in any three-month period without registration in compliance with Rule 144 or a similar exemption under the Securities Act and (b) at such time that our common stock is trading on a national securities exchange and all of the holder's registrable securities can be sold during a three-month period without registration.

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Registration Rights Agreement

Pursuant to the Post-IPO RRA between us and each of Baker Brothers and its affiliates, OrbiMed and its affiliates and Kris Vaddi, the RRA Investors are entitled to rights with respect to the registration of their shares under the Securities Act that supersede such rights as described above held by the RRA Investors under the IRA. These registration rights include the right to demand that we file with the SEC a Form S-3 registration statement (except if we are not then eligible to register for resale the registrable securities on Form S-3, in which case, such registration shall be on another appropriate form in accordance with the Securities Act) covering the registration of their registrable securities for resale, subject to certain conditions, as well as rights to be permitted an aggregate of five underwritten public offerings between the RRA Investors during the term of the Post-IPO RRA, subject to a limitation of an aggregate of two underwritten public offerings per calendar year, to effect the sale of their common stock for sale. The RRA Investors also have piggy-back rights to participate in registrations demanded by any of the other RRA Investors. The Post-IPO RRA requires us to pay expenses relating to such registrations and indemnify these holders against certain liabilities. Our registration obligations under this registration rights agreement would continue in effect until the earliest of (i) December 20, 2030, (ii) when the applicable registrable securities have been resold by the holders pursuant to an effective registration statement, (iii) when the applicable registrable securities have been resold pursuant to Rule 144 or (iv) when the applicable registrable securities may be resold pursuant to Rule 144 without limitations as to volume or manner of sale.

Anti-Takeover Provisions

The provisions of Delaware General Corporation Law, or DGCL, our restated certificate of incorporation and our restated bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of our company. These provisions, which are summarized below, may have the effect of discouraging takeover bids. They are also designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging a proposal to acquire us because negotiation of these proposals could result in an improvement of their terms.

Delaware Law

We are subject to the provisions of Section 203 of the DGCL regulating corporate takeovers. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a “business combination” with an “interested stockholder” for a period of three years following the date on which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, (i) shares owned by persons who are directors and also officers and (ii) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66.67% of the outstanding voting stock that is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction or series of transactions together resulting in a financial benefit to the interested stockholder. An interested stockholder is a

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person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. We expect the existence of this provision to have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. We also anticipate that Section 203 may also discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

Anti-Takeover Effects of Certain Provisions of Our Restated Certificate of Incorporation and Restated Bylaw

Our restated certificate of incorporation and our restated bylaws include a number of provisions that could deter hostile takeovers or delay or prevent changes in control of our company, including the following:

- ***Board of Directors Vacancies.*** Our restated certificate of incorporation and restated bylaws authorizes only our board of directors to fill vacant directorships, including newly created seats. In addition, the number of directors constituting our board of directors is permitted to be set only by a resolution adopted by a majority vote of our entire board of directors. These provisions would prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.
- ***Classified Board.*** Our restated certificate of incorporation and restated bylaws provide that our board of directors is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors. See the section entitled "Management—Board Composition."
- ***Stockholder Action; Special Meetings of Stockholders.*** Our restated certificate of incorporation provide that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock would not be able to amend our restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our restated bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, our Chief Executive Officer or our President, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.
- ***Advance Notice Requirements for Stockholder Proposals and Director Nominations.*** Our restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our restated bylaws also specify certain requirements regarding the form and content of a stockholder's notice. These provisions might preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions might also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.
- ***No Cumulative Voting.*** The DGCL provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our restated certificate of incorporation and restated bylaws do not provide for cumulative voting.
- ***Directors Removed Only for Cause.*** Our restated certificate of incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of the holders of at least two-thirds of our outstanding common stock.

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- *Amendment of Charter Provisions.* Any amendment of the above provisions in our restated certificate of incorporation would require approval by holders of at least two-thirds of our outstanding common stock.
- *Issuance of Undesignated Preferred Stock.* Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock would enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by merger, tender offer, proxy contest or other means.
- *Choice of Forum.* Our restated certificate of incorporation provides that, to the fullest extent permitted by law, the Court of Chancery of the State of Delaware will be the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our restated certificate of incorporation or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable. Our restated bylaws also provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court which recently found that such provisions are facially valid under Delaware law or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court. Neither the exclusive forum provision nor the Federal Forum Provision applies to suits brought to enforce any duty or liability created by the Exchange Act. Section 27 of the Exchange Act creates exclusive federal jurisdiction over all claims brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. Accordingly, actions by our stockholders to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder also must be brought in federal court. Our stockholders will not be deemed to have waived our compliance with the federal securities laws and the regulations promulgated thereunder. Any person or entity purchasing or otherwise acquiring or holding any interest in any of our securities shall be deemed to have notice of and consented to our exclusive forum provisions, including the Federal Forum Provision. These provisions may limit a stockholder's ability to bring a claim in a judicial forum of their choosing for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock and non-voting common stock is Computershare Trust Company, N.A.

The Nasdaq Global Select Market Listing

Our common stock is listed on The Nasdaq Global Select Market under the symbol "PRLD." The non-voting common stock will not be listed for trading on any securities exchange.

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SHARES ELIGIBLE FOR FUTURE SALE

Sales of substantial amounts of our common stock, including shares issued upon exercise of outstanding options and warrants, in the public market could adversely affect market prices prevailing from time to time and could impair our ability to raise capital through the sale of our equity securities. See “Risk Factors—Risks Related to Ownership of Our Common Stock and This Offering—A sale of a substantial number of shares of our common stock may cause the price of our common stock to decline.”

Based on the number of shares of common stock outstanding as of September 30, 2020, upon the completion of this offering, we will have a total of _____ shares of our common stock outstanding, assuming the issuance of _____ shares of common stock in this offering. Of these outstanding shares, all of the shares of common stock sold in this offering and all 9,573,750 shares of common stock sold by us in our initial public offering will be freely tradable, except that any shares purchased in this offering by our affiliates, as that term is defined in Rule 144 under the Securities Act can only be sold in compliance with the Rule 144 limitations described below or in compliance with the lock-up agreements.

The remaining outstanding shares of our common stock and our non-voting common stock will be deemed “restricted securities” as defined in Rule 144. Restricted securities may be sold in the public market only if they are registered under the Securities Act or if they qualify for an exemption from registration under Rule 144 or Rule 701 promulgated under the Securities Act, which rules are summarized below.

Lock-Up/Market Standoff Agreements

In connection with our IPO, all of our directors and officers and substantially all of our security holders from prior to our IPO entered into lock-up agreements or market standoff provisions that prohibit them from offering for sale, selling, contracting to sell, granting any option for the sale of, transferring or otherwise disposing of any shares of our common stock, options or warrants to acquire shares of our common stock or any security or instrument related to our common stock, or entering into any swap, hedge or other arrangement that transfers any of the economic consequences of ownership of our common stock, including, with respect to all of the foregoing, shares of our non-voting common stock, through March 23, 2021 without the prior written consent of Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc., subject to certain exceptions. Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. may, in their sole discretion and at any time or from time to time before the termination of the 180-day period release all or any portion of the securities subject to lock-up agreements. See the section entitled “Underwriters.”

In addition, in connection with this offering, all of our directors and officers, certain significant stockholders and certain affiliates entered into lock-up agreements or market standoff provisions that prohibit them from offering for sale, selling, contracting to sell, granting any option for the sale of, transferring or otherwise disposing of any shares of our common stock, options or warrants to acquire shares of our common stock or any security or instrument related to our common stock, or entering into any swap, hedge or other arrangement that transfers any of the economic consequences of ownership of our common stock, including, with respect to all of the foregoing, shares of our non-voting common stock, until 90 days following the date of this prospectus, without the prior written consent of Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc., subject to certain exceptions. Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. may, in their sole discretion and at any time or from time to time before the termination of the 180-day period release all or any portion of the securities subject to lock-up agreements. See the section entitled “Underwriters.”

Rule 144

In general, under Rule 144 as currently in effect, a person who is not deemed to have been one of our affiliates for purposes of the Securities Act at any time during the 90 days preceding a sale and who has

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beneficially owned the shares proposed to be sold for at least six months, including the holding period of any prior owner other than our affiliates, is entitled to sell those shares without complying with the manner of sale, volume limitation or notice provisions of Rule 144, subject to compliance with the public information requirements of Rule 144. If such a person has beneficially owned the shares proposed to be sold for at least one year, including the holding period of any prior owner other than our affiliates, then that person would be entitled to sell those shares without complying with any of the requirements of Rule 144.

In general, under Rule 144, as currently in effect, our affiliates or persons selling shares on behalf of our affiliates are entitled to sell upon expiration of the lock-up and market standoff agreements described above, within any three-month period, a number of shares that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately shares immediately after this offering assuming no exercise of the underwriters' option to purchase additional shares; or
- the average reported weekly trading volume of our common stock on Nasdaq during the four calendar weeks preceding the filing of a notice on Form 144 with respect to that sale.

Sales under Rule 144 by our affiliates or persons selling shares on behalf of our affiliates are also subject to certain manner of sale provisions and notice requirements and to the availability of current public information about us.

Rule 701

Rule 701 generally allows a stockholder who purchased shares of our common stock pursuant to a written compensatory plan or contract and who is not deemed to have been an affiliate of our company during the immediately preceding 90 days to sell these shares in reliance upon Rule 144, but without being required to comply with the public information, holding period, volume limitation or notice provisions of Rule 144. Rule 701 also permits affiliates of our company to sell their Rule 701 shares under Rule 144 without complying with the holding period requirements of Rule 144. All holders of Rule 701 shares are subject to the lock-up and market standoff agreements described above.

Registration Rights

We have granted demand, piggyback and Form S-3 registration rights to certain of our stockholders to sell our common stock. Registration of the sale of these shares under the Securities Act would result in these shares becoming freely tradable without restriction under the Securities Act immediately upon the effectiveness of the registration, except for shares purchased by affiliates. For a further description of these rights, see the section entitled "Description of Capital Stock—Registration Rights."

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MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income taxes, does not discuss the potential application of the alternative minimum tax, the special tax accounting rules under Section 451(b) of the Code, or the Medicare Contribution tax on net investment income and does not deal with state or local tax laws, U.S. federal non-income tax laws, such as gift and estate tax laws, except to the limited extent provided below, or any non-U.S. tax laws that may be relevant to Non-U.S. Holders in light of their particular circumstances.

Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as:

- insurance companies, banks, investment funds and other financial institutions;
- tax-exempt organizations (including private foundations) and tax-qualified retirement plans;
- foreign governments and international organizations;
- broker-dealers and traders in securities;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- “qualified foreign pension funds” as defined in Section 897(l)(2) of the Code and entities of all of the interests of which are held by qualified foreign pension funds;
- persons that own, or are deemed to own, more than 5% of our capital stock;
- “controlled foreign corporations,” “passive foreign investment companies” and corporations that accumulate earnings to avoid U.S. federal income tax;
- persons that hold our common stock as part of a “straddle,” “hedge,” “conversion transaction,” “synthetic security” or integrated investment or other risk reduction strategy;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes); and
- partnerships and other entities or arrangements treated as pass-through or disregarded entities for U.S. federal income tax purposes, and investors in such entities (regardless of their places of organization or formation).

Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them.

Furthermore, the discussion below is based upon the provisions of the Code, and U.S. Treasury Regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, possibly retroactively, or could be subject to differing interpretations which could result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the Internal Revenue Service, or the IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will not take a contrary position regarding the tax consequences described herein, or that any such contrary position would not be sustained by a court.

PERSONS CONSIDERING THE PURCHASE OF OUR COMMON STOCK PURSUANT TO THIS OFFERING SHOULD CONSULT THEIR OWN TAX ADVISORS CONCERNING THE U.S. FEDERAL INCOME TAX CONSEQUENCES OF ACQUIRING, OWNING AND DISPOSING OF OUR COMMON STOCK IN LIGHT OF THEIR PARTICULAR SITUATIONS AS WELL AS ANY CONSEQUENCES ARISING UNDER THE LAWS OF ANY OTHER TAXING JURISDICTION, INCLUDING ANY STATE, LOCAL OR NON-U.S. TAX CONSEQUENCES OR ANY U.S. FEDERAL NON-INCOME TAX CONSEQUENCES, AND THE POSSIBLE APPLICATION OF TAX TREATIES.

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For the purposes of this discussion, a “Non-U.S. Holder” is a beneficial owner of common stock, other than a partnership or other entity or arrangement treated as a pass-through entity, that is not, for U.S. federal income tax purposes, (a) an individual who is a citizen or resident of the United States, (b) a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes), created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate, the income of which is subject to U.S. federal income taxation regardless of its source, or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons (within the meaning of Section 7701(a)(30) of the Code) have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

If you are an individual non-U.S. citizen, you may, in some cases, be deemed to be a resident alien (as opposed to a nonresident alien) by virtue of being present in the United States for at least 31 days in the calendar year and for an aggregate of at least 183 days during a three-year period ending in the current calendar year. Generally, for this purpose, all the days present in the current year, one-third of the days present in the immediately preceding year, and one-sixth of the days present in the second preceding year, are counted.

Resident aliens are generally subject to U.S. federal income tax as if they were U.S. citizens. Individuals who are uncertain of their status as resident or nonresident aliens for U.S. federal income tax purposes are urged to consult their own tax advisors regarding the U.S. federal income tax consequences of the ownership or disposition of our common stock.

Distributions

We do not expect to make any distributions on our common stock in the foreseeable future. If we do make distributions on our common stock, however, such distributions will constitute dividends for U.S. tax purposes to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Distributions in excess of our current and accumulated earnings and profits will constitute a return of capital that is applied against and reduces, but not below zero, a Non-U.S. Holder’s adjusted tax basis in our common stock. Any remaining excess will be treated as gain realized on the sale or exchange of our common stock as described below under the section entitled “—Gain on Disposition of Our Common Stock.”

Any distribution on our common stock that is treated as a dividend paid to a Non-U.S. Holder that is not effectively connected with the Non-U.S. Holder’s conduct of a trade or business in the United States will generally be subject to U.S. federal withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and the Non-U.S. Holder’s country of residence. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide the applicable withholding agent with a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E or other appropriate form, certifying the Non-U.S. Holder’s entitlement to benefits under that treaty. Such form must be provided prior to the payment of dividends and must be updated periodically. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder’s behalf, the holder will be required to provide appropriate documentation to such agent. The holder’s agent may then be required to provide certification to the applicable withholding agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. withholding tax under an income tax treaty, you should consult with your own tax advisor to determine if you are able to obtain a refund of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that the holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to the applicable withholding agent. In general, such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the same rates applicable to U.S. persons. A corporate Non-U.S.

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Holder receiving effectively connected dividends may also be subject to an additional “branch profits tax,” which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder’s effectively connected earnings and profits, subject to certain adjustments.

See also the section below entitled “—Foreign Accounts” for additional withholding rules that may apply to dividends paid to certain foreign financial institutions or non-financial foreign entities.

Gain on Disposition of Our Common Stock

Subject to the discussions below under the sections entitled “—Backup Withholding and Information Reporting” and “—Foreign Accounts,” a Non-U.S. Holder generally will not be subject to U.S. federal income or withholding tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of the Non-U.S. Holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that the holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien who is an individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a “United States real property holding corporation” within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or the Non-U.S. Holder’s holding period in the common stock.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at the same U.S. federal income tax rates applicable to U.S. persons. Corporate Non-U.S. Holders described in (a) above may also be subject to the additional branch profits tax at a 30% rate (or such lower rate as may be specified by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year, as adjusted for certain items. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by certain U.S. source capital losses (even though you are not considered a resident of the United States), provided you have timely filed U.S. federal income tax returns with respect to such losses. With respect to (c) above, in general, we would be a United States real property holding corporation if U.S. real property interests as defined in the Code and the U.S. Treasury Regulations comprised (by fair market value) at least half of our worldwide real property interests plus our other assets used or held for use in a trade or business. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. However, there can be no assurance that we will not become a United States real property holding corporation in the future. Even if we were to be treated as a U.S. real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock would not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly or constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the Non-U.S. Holder’s holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will qualify as regularly traded on an established securities market.

U.S. Federal Estate Tax

The estates of nonresident alien individuals generally are subject to U.S. federal estate tax on property with a U.S. situs. Because we are a U.S. corporation, our common stock will be U.S. situs property and, therefore, will be included in the taxable estate of a nonresident alien decedent, unless an applicable estate tax treaty between the United States and the decedent’s country of residence provides otherwise. The terms “resident” and “nonresident” are defined differently for U.S. federal estate tax purposes than for U.S. federal income tax purposes. Investors are urged to consult their own tax advisors regarding the U.S. federal estate tax consequences of the ownership or disposition of our common stock.

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Backup Withholding and Information Reporting

Generally, we or certain financial middlemen must report information to the IRS with respect to any dividends we pay on our common stock including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. federal backup withholding. U.S. federal backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E, or IRS Form ECI, as applicable, or otherwise establishes an exemption, provided that the applicable withholding agent does not have actual knowledge or reason to know the holder is a U.S. person.

Under current U.S. federal income tax law, U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or non-U.S., unless the Non-U.S. Holder provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E, or IRS Form ECI, as applicable, or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Backup withholding is not an additional tax. If backup withholding is applied to you, you should consult with your own tax advisor to determine whether you have overpaid your U.S. federal income tax, and whether you are able to obtain a tax refund or credit of the overpaid amount.

Foreign Accounts

In addition, U.S. federal withholding taxes may apply under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments, including dividends paid to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends on our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution agrees to undertake certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. The 30% federal withholding tax described in this paragraph cannot be reduced under an income tax treaty with the United States. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States-owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules. Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally also would apply to payments of gross proceeds from the sale or other disposition of common stock. Under proposed regulations, however, no withholding will apply with respect to payments of gross proceeds. The preamble to the proposed regulations specifies that taxpayers are permitted to rely on such proposed regulations pending finalization.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

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EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW, AS WELL AS TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL, NON-U.S. OR U.S. FEDERAL NON-INCOME TAX LAWS SUCH AS ESTATE AND GIFT TAX OR UNDER ANY APPLICABLE TAX TREATY.

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UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus, the underwriters named below, for whom Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares of common stock indicated below:

<u>Name</u>	<u>Number of Shares of Common Stock</u>
Morgan Stanley & Co. LLC	
Goldman Sachs & Co. LLC	
BofA Securities, Inc.	
Total:	

The underwriters and the representatives are collectively referred to as the “underwriters” and the “representatives,” respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters’ option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus and part to certain dealers at a price that represents a concession not in excess of \$ per share of common stock under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to additional shares at the public offering price listed on the cover page of this prospectus, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter’s name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters’ option to purchase up to an additional shares.

	<u>Per Share of Common Stock</u>	<u>Total</u>	
		<u>No Exercise</u>	<u>Full Exercise</u>
Public offering price	\$	\$	\$
Underwriting discounts and commissions to be paid by us:	\$	\$	\$
Proceeds, before expenses, to us	\$	\$	\$

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$ million. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority of up to \$.

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Our common stock is listed on The Nasdaq Global Select Market under the trading symbol “PRLD”. The non-voting common stock is not listed on any national securities exchange.

We and all directors and officers and certain stockholders have agreed that, without the prior written consent of Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. on behalf of the underwriters, we and they will not, and will not publicly disclose an intention to, during the period ending 90 days after the date of this prospectus, or the restricted period:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or non-voting common stock or any securities convertible into or exercisable or exchangeable for shares of common stock or non-voting common stock;
- file any registration statement with the SEC relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock or non-voting common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock or non-voting common stock;

whether any such transaction described above is to be settled by delivery of common stock, non-voting common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to our directors, officers and securityholders with respect to:

- transactions relating to shares of common stock or other securities acquired in the offering or in open market transactions after the completion of the offering, provided that no filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made during the restricted period in connection with subsequent sales of common stock or other securities acquired in the offering or such open market transactions;
- transfers or dispositions of shares of common stock or any security convertible into or exercisable or exchangeable for common stock (i) as a bona fide gift or charitable contribution, (ii) by will or intestacy or to any member of the holder’s immediate family or to a trust for the direct or indirect benefit of the holder and/or any member of the holder’s immediate family, (iii) to any corporation, partnership, limited liability company or other business entity, all of the beneficial ownership interests of which, in each such case, are held by the holder or any member of the holder’s immediate family, (iv) if the holder is an entity, to limited partners, members, shareholders or holders of similar equity interests in the holder, or (v) if the holder is an entity, to another corporation, partnership, limited liability company, trust or other business entity that is an affiliate (as defined in Rule 405 promulgated under the Securities Act) of the holder, or to any investment fund or other entity controlled or managed by the holder or affiliated with the holder; provided that, in the case of any transfer or distribution pursuant to this clause, (A) each transferee, donee or distributee shall sign and deliver a substantially similar lock-up agreement and (B) no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of common stock or any securities convertible into or exercisable or exchangeable for common stock shall be required or shall be voluntarily made during the restricted period (other than, in the case of a transfer or other disposition pursuant to clause (i) or (ii) above, a Form 5 required to be filed under the Exchange Act if the holder is subject to Section 16

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reporting under the Exchange Act; any such filing will indicate by footnote disclosure or otherwise the nature of the transfer or disposition); and provided further that any such transfer pursuant to this clause shall not involve a transfer or distribution for value;

- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for shares of common stock by operation of law pursuant to a qualified domestic order or other court order or in connection with a divorce settlement; provided that (i) any filing under Section 16(a) of the Exchange Act made during the restricted period shall clearly indicate in the footnotes thereto that (A) the filing relates to the circumstances described in this clause and (B) no securities were sold by the holder, and (ii) the holder does not otherwise voluntarily effect any other public filing or report regarding such transfers during the restricted period;
- (i) the exercise of options or other similar awards or the vesting or settlement of awards granted pursuant to our equity incentive plans as described in this prospectus and outstanding on the date of the underwriting agreement (including the delivery and receipt of shares of common stock, other awards or any securities convertible into or exercisable or exchangeable for shares of common stock in connection with such exercise, vesting or settlement), or (ii) the transfer or disposition of shares of common stock or any securities convertible into shares of common stock by the holder to the company (or the purchase and cancellation of the same by the company) upon a vesting or settlement event of our securities or upon the exercise of options to purchase our securities on a “cashless” or “net exercise” basis solely to the extent permitted by the instruments representing such options pursuant to our equity incentive plans as described in this prospectus and solely to cover withholding tax obligations in connection with such transaction and any transfer to the company for the payment of taxes as a result of such transaction, provided that (A) the shares of common stock received upon the exercise or settlement of the option are subject to the same restrictions, (B) no public disclosure or filing under Section 16(a) of the Exchange Act shall be voluntarily made during the restricted period and (C) to the extent a filing under Section 16(a) of the Exchange Act is required during the restricted period as a result of transfers in this clause, it shall clearly indicate that the filing relates to the circumstances described in this clause;
- transfers to the company pursuant to the repurchase of shares of common stock in connection with the termination of the holder’s employment with the company or other service relationship with the company pursuant to contractual agreements with the company as in effect as of the date of this prospectus, provided that no public disclosure or filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made during the restricted period;
- facilitating the establishment of a trading plan on behalf of a stockholder, officer or director pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required of or voluntarily made by or on behalf of the holder or the company regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period; or
- transfers pursuant to a bona fide third-party tender offer for all outstanding shares of common stock or securities convertible into or exercisable or exchangeable for shares of common stock, merger, amalgamation, consolidation or other similar transaction approved by our board of directors and made to all holders of our securities involving a “change of control” (as defined in the lock-up agreement) of the company (including, without limitation, the entering into any lock-up, voting or similar agreement pursuant to which the holder may agree to transfer, sell, tender or otherwise dispose of shares of common stock or other such securities in connection with such transaction, or vote any shares of common stock or other such securities in favor of any such transaction); provided that in the event that such tender offer, merger, amalgamation, consolidation or other such transaction is not completed, such securities held by the holder shall remain subject to the same restrictions.

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The restrictions on transfers or other dispositions by us described above do not apply to:

- the shares to be sold in this offering;
- the issuance by us of shares of common stock or securities convertible into or exercisable for shares of common stock upon the exercise of an option or warrant or the conversion of a security outstanding on the date of this prospectus and described herein;
- the issuance by us of shares of common stock or non-voting common stock upon the exchange of any security exchangeable therefor or the conversion of any security convertible therefor pursuant to a contractual arrangement or other right described herein, provided that each recipient of such issuance executes and delivers a lock-up agreement;
- facilitating the establishment of a trading plan on behalf of one of our shareholders, officers or directors pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for the transfer of common stock during the restricted period and, to the extent a public announcement or filing under the Exchange Act is required of or voluntarily made by us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period;
- the grant of any options to purchase shares of common stock or other awards granted under a stock incentive plan or stock purchase plan described in this prospectus, and the issuance by us of shares of common stock upon the exercise thereof, provided that each recipient of such grant executes and delivers a lock-up agreement;
- our filing of any registration statement on Form S-8 or a successor form relating to the shares of common stock granted pursuant to or reserved for issuance under a stock incentive plan or stock purchase plan described in this prospectus; or
- shares of common stock or other securities issued in connection with a transaction with an unaffiliated third party that includes a debt financing or a bona fide commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements, or intellectual property license agreements) or any acquisition of assets or acquisition of not less than a majority or controlling portion of the equity of another entity, provided that (1) the aggregate number of shares issued does not exceed 5% of the total number of outstanding shares of our common stock immediately following the closing of this offering and (2) the recipient of any such shares during the restricted period enters into a lock-up agreement.

Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc., in their joint discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In connection with our initial public offering, we and all of our directors and executive officers and substantially all of our stockholders agreed to 180 day lock-up agreements on substantially the same terms as the 90 day lock-up agreements for this offering. Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. have waived the lock-up agreement from our initial public offering to the extent necessary to permit us to sell shares of our common stock in this offering.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess

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of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses. For example, certain of the underwriters also served as underwriters in our initial public offering in September 2020.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling Restrictions

Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

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Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

European Economic Area

In relation to each Member State of the European Economic Area and the United Kingdom, or each, a Relevant State, no securities have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the securities which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of securities may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- (a) to any legal entity which is a qualified investor as defined under the Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the representatives; or
- (c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of shares shall require us or any of our representatives to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression an “offer to the public” in relation to any shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase any shares, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129 (as amended).

United Kingdom

Each underwriter has represented and agreed that:

- (a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, or FSMA, received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and
- (b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Hong Kong

Shares of our common stock may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), (ii) to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder or (iii) in other circumstances which do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to shares of our common stock may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong

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or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares of our common stock which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder.

Japan

No registration pursuant to Article 4, paragraph 1 of the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended), or the FIEL has been made or will be made with respect to the solicitation of the application for the acquisition of the shares of common stock.

Accordingly, the shares of common stock have not been, directly or indirectly, offered or sold and will not be, directly or indirectly, offered or sold in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan) or to others for re-offering or re-sale, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan except pursuant to an exemption from the registration requirements, and otherwise in compliance with, the FIEL and the other applicable laws and regulations of Japan.

For Qualified Institutional Investors, or QII

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a “QII only private placement” or a “QII only secondary distribution” (each as described in Paragraph 1, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred to QIIs.

For Non-QII Investors

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a “small number private placement” or a “small number private secondary distribution” (each as is described in Paragraph 4, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred en bloc without subdivision to a single investor.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of shares of our common stock may not be circulated or distributed, nor may the shares of our common stock be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where shares of our common stock are subscribed or purchased under Section 275 by a relevant person which is: (i) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (ii) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments

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and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired shares of our common stock under Section 275 except: (a) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (b) where no consideration is given for the transfer; or (c) by operation of law.

Notice to Prospective Investors in Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA ("FINMA"), and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes ("CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission, in relation to the offering. This prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001, or Corporations Act, and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons, or Exempt Investors, who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

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The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Israel

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728—1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728—1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the “Addressed Investors”); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728—1968, subject to certain conditions (the “Qualified Investors”). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728—1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728—1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728—1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728—1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728—1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor’s name, address and passport number or Israeli identification number.

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LEGAL MATTERS

The validity of the shares of common stock offered by this prospectus will be passed upon for us by Fenwick & West LLP, San Francisco, California. Cooley LLP, Boston, Massachusetts, is acting as counsel for the underwriters in connection with this offering.

EXPERTS

The financial statements of Prelude Therapeutics Incorporated at December 31, 2019 and 2018, and for each of the two years in the period ended December 31, 2019, appearing in this prospectus and registration statement have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company's ability to continue as a going concern as described in Note 2 to the financial statements) appearing elsewhere herein, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

ADDITIONAL INFORMATION

We have filed with the SEC a registration statement on Form S-1 (File Number 333-) under the Securities Act with respect to the shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits filed therewith. For further information about us and the common stock offered hereby, reference is made to the registration statement and the exhibits filed therewith. Statements contained in this prospectus concerning the contents of any contract or any other document are not necessarily complete, please see the copy of the contract or document that has been filed for the complete contents of that contract or document. Each statement in this prospectus relating to a contract or document filed as an exhibit is qualified in all respects by the filed exhibit. The exhibits to the registration statement should be reviewed for the complete contents of these contracts and documents.

We file periodic reports, proxy statements and other information with the SEC pursuant to the Securities Exchange Act of 1934, as amended. The SEC maintains a website that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC. The address of the website is www.sec.gov.

We also maintain a website at www.preludetx.com. You may access these materials at our website free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. Information contained in, or that can be accessed through, our website is not a part of, and is not incorporated into, this prospectus.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Prelude Therapeutics Incorporated

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Prelude Therapeutics Incorporated (the Company) as of December 31, 2019 and 2018, the related statements of operations, changes in convertible preferred stock and stockholders' deficit and cash flows for the years then ended, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2019 and 2018, and the results of its operations and its cash flows for the years then ended in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 2 to the financial statements, the Company has recurring losses from operations and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 2. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2019.

Philadelphia, Pennsylvania

July 23, 2020, except for the reverse stock split described in Note 11, as to which the date is September 21, 2020

**Confidential Treatment Requested by Prelude Therapeutics Incorporated
Pursuant To 17 C.F.R. Section 200.83**

PRELUDE THERAPEUTICS INCORPORATED

BALANCE SHEETS

<u>(in thousands, except share and per share data)</u>	<u>December 31,</u>	
	<u>2018</u>	<u>2019</u>
Assets		
Current assets:		
Cash and cash equivalents	\$ 15,595	\$ 18,879
Prepaid expenses and other current assets	—	1,345
Total current assets	<u>15,595</u>	<u>20,224</u>
Property and equipment, net	811	1,647
Total assets	<u>\$ 16,406</u>	<u>\$ 21,871</u>
Liabilities, convertible preferred stock and stockholders' deficit		
Current liabilities:		
Capital lease obligation	\$ —	\$ 258
Accounts payable	1,362	1,974
Accrued expenses and other current liabilities	1,085	2,603
Total current liabilities	<u>2,447</u>	<u>4,835</u>
Other liabilities	57	5
Total liabilities	<u>2,504</u>	<u>4,840</u>
Convertible preferred stock, \$0.0001 par value:		
Series A convertible preferred stock: 13,574,008 shares authorized at December 31, 2019; 11,736,119 shares issued and outstanding at December 31, 2018 and 2019 (liquidation value of \$36,878 at December 31, 2019)	36,595	36,595
Series B convertible preferred stock: 18,500,000 shares authorized at December 31, 2019; no shares and 7,628,846 shares issued and outstanding at December 31, 2018 and 2019, respectively (liquidation value of \$30,000 at December 31, 2019)	—	29,848
Total convertible preferred stock	<u>36,595</u>	<u>66,443</u>
Commitments (note 7)		
Stockholders' deficit:		
Common stock, \$0.0001 par value: 42,000,000 shares authorized at December 31, 2019; 2,380,270 and 3,161,653 shares issued and outstanding at December 31, 2018 and 2019, respectively	—	—
Additional paid-in capital	234	1,085
Accumulated deficit	<u>(22,927)</u>	<u>(50,497)</u>
Total stockholders' deficit	<u>(22,693)</u>	<u>(49,412)</u>
Total liabilities, convertible preferred stock and stockholders' deficit	<u>\$ 16,406</u>	<u>\$ 21,871</u>

See accompanying notes to financial statements.

**Confidential Treatment Requested by Prelude Therapeutics Incorporated
Pursuant To 17 C.F.R. Section 200.83**

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF OPERATIONS

<u>(in thousands, except share and per share data)</u>	<u>Year ended December 31,</u>	
	<u>2018</u>	<u>2019</u>
Operating expenses:		
Research and development	\$ 12,621	\$ 24,279
General and administrative	2,354	3,830
Total operating expenses	<u>14,975</u>	<u>28,109</u>
Loss from operations	(14,975)	(28,109)
Other income, net	295	539
Net loss	<u>\$ (14,680)</u>	<u>\$ (27,570)</u>
Per share information:		
Net loss per share of common stock, basic and diluted	<u>\$ (10.46)</u>	<u>\$ (16.52)</u>
Weighted average common shares outstanding, basic and diluted	<u>1,402,928</u>	<u>1,668,549</u>
Pro forma net loss per share of common stock, basic and diluted (unaudited)		<u>\$ (0.86)</u>
Pro forma weighted average shares outstanding, basic and diluted (unaudited).		<u>32,105,972</u>

See accompanying notes to financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF CHANGES IN CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' DEFICIT

(in thousands, except shares)	Convertible preferred stock				Stockholders' deficit				
	Series A		Series B		Common stock		Additional paid-in capital	Accumulated deficit	Total
	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at January 1, 2018	6,007,743	\$18,658	—	\$ —	1,866,367	\$ —	\$ 54	\$ (8,247)	\$ (8,193)
Sale of Series A convertible preferred stock, net of issuance costs of \$63	5,728,376	17,937	—	—	—	—	—	—	—
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	513,903	—	180	—	180
Net loss	—	—	—	—	—	—	—	(14,680)	(14,680)
Balance at December 31, 2018	11,736,119	36,595	—	—	2,380,270	—	234	(22,927)	(22,693)
Exercise of stock options	—	—	—	—	3,242	—	5	—	5
Sale of Series B convertible preferred stock, net of issuance costs of \$152	—	—	7,628,846	29,848	—	—	—	—	—
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	778,141	—	846	—	846
Net loss	—	—	—	—	—	—	—	(27,570)	(27,570)
Balance at December 31, 2019	<u>11,736,119</u>	<u>\$36,595</u>	<u>7,628,846</u>	<u>\$29,848</u>	<u>3,161,653</u>	<u>\$ —</u>	<u>\$ 1,085</u>	<u>\$ (50,497)</u>	<u>\$(49,412)</u>

See accompanying notes to financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF CASH FLOWS

<u>(in thousands)</u>	Year ended December 31,	
	2018	2019
Cash flows used in operating activities:		
Net loss	\$(14,680)	\$(27,570)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	149	382
Loss on disposal of property and equipment	15	10
Stock-based compensation	180	846
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	66	(1,345)
Accounts payable	721	546
Accrued expenses and other liabilities	595	1,466
Net cash used in operating activities	(12,954)	(25,665)
Cash flows used in investing activities:		
Purchases of property and equipment	(529)	(780)
Net cash used in investing activities	(529)	(780)
Cash flows provided by financing activities:		
Proceeds from the sale of Series A convertible preferred stock, net	17,937	—
Proceeds from the sale of Series B convertible preferred stock, net	—	29,848
Payment of capital lease obligation	—	(124)
Proceeds from the exercise of stock options	—	5
Net cash provided by financing activities	17,937	29,729
Net increase in cash and cash equivalents	4,454	3,284
Cash and cash equivalents at beginning of year	11,141	15,595
Cash and cash equivalents at end of year	\$ 15,595	\$ 18,879
Supplemental disclosures:		
Issuance of capital lease obligation in connection with purchase of property and equipment	\$ —	\$ 382
Property and equipment in accounts payable	\$ 6	\$ 66

See accompanying notes to financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

NOTES TO FINANCIAL STATEMENTS

1. Nature of Operations

Prelude Therapeutics Incorporated (the “Company”) was incorporated in Delaware on February 5, 2016 and is a clinical-stage biotechnology company focused on discovering and developing new medicines targeting chromatin function to treat cancer and rare diseases. Since beginning operations, the Company has devoted substantially all its efforts to research and development, conducting preclinical and clinical studies, recruiting management and technical staff, administration, and raising capital.

2. Risks and Liquidity

The Company is subject to a number of risks common to early-stage companies in the biotechnology industry. Principal among these risks are the uncertainties in the development process, development of the same or similar technological innovations by competitors, protection of proprietary technology, dependence on key personnel, compliance with government regulations and approval requirements, and the need to obtain additional financing to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive pre-clinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure, and extensive compliance-reporting capabilities. There can be no assurance that the Company’s research and development will be successfully completed, that adequate protection for the Company’s technology will be obtained, that any products developed will obtain necessary government regulatory approval, or that any approved products will be commercially viable. The Company operates in an environment of rapid change in technology and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and contractors.

The Company follows the provisions of Financial Accounting Standards Board (“FASB”) Accounting Standards Codification (“ASC”) Topic 205-40, Presentation of Financial Statements—Going Concern, which requires management to assess the Company’s ability to continue as a going concern within one year after the date the financial statements are issued.

Since its inception, the Company has incurred operating losses and has an accumulated deficit of \$50.5 million at December 31, 2019. The Company has no revenue to date and devotes its efforts to research and development. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates currently in development. The Company’s activities have been primarily funded by the sale of Convertible Preferred Stock (Note 8). These factors and the Company’s recurring losses from operations, negative cash from operations, and accumulated deficit since inception raise substantial doubt about the Company’s ability to continue as a going concern within one year after the date these financial statements are issued.

The Company’s cash and cash equivalents at December 31, 2019 were \$18.9 million. This, combined with approximately \$29.9 million raised through a Series B Preferred stock financing in March 2020 (Note 11) is expected to enable the Company to fund its operating expenses and capital expenditure requirements into December 2020, at which time the Company will need to secure additional funding in the future, from one or more equity or debt financings, collaborations, or other sources, in order to carry out all of its planned research and development and commercialization activities. However, there is no assurance that the Company will be able to obtain additional equity under acceptable terms, if at all. If the Company is unable to obtain additional financing, the lack of liquidity could have a material adverse effect on the Company’s future prospects. As a result of these factors, there is substantial doubt about the Company’s ability to continue as a going concern within one year after the date that these financial statements are issued.

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PRELUDE THERAPEUTICS INCORPORATED

NOTES TO FINANCIAL STATEMENTS

The accompanying financial statements have been prepared on a going-concern basis, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. The financial statements do not include any adjustments related to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of this uncertainty. Management is currently evaluating different strategies to obtain the required funding of future operations. These strategies may include, but are not limited to, additional funding from current investors, funding from new investors including strategic corporate investors, and an initial public offering of the Company's common stock. There can be no assurance these future funding efforts will be successful.

3. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying financial statements have been prepared in accordance with accounting principles generally accepted in the United States ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") promulgated by the Financial Accounting Standards Board ("FASB").

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and contingent liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

Estimates and assumptions are periodically reviewed and the effects of the revisions are reflected in the accompanying financial statements in the period they are determined to be necessary. Significant areas that require management's estimates include the fair value of the Company's common stock, stock-based compensation assumptions, and accrued clinical trial expenses.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist of cash and cash equivalents. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and believes it is not exposed to significant credit risk beyond the normal credit risk associated with commercial banking relationships.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views and manages its operations as a single operating segment.

Fair Value of Financial Instruments

Management believes that the carrying amounts of the Company's financial instruments, including cash, accounts payable, accrued expenses and a capital lease obligation, approximate fair value due to the short-term nature of these instruments.

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PRELUDE THERAPEUTICS INCORPORATED

NOTES TO FINANCIAL STATEMENTS

Cash Equivalents

The Company's cash equivalents include short-term highly liquid investments with an original maturity of 90 days or less when purchased and are carried at fair value in the accompanying balance sheets.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation expense is recognized using the straight-line method over the estimated useful life of the asset, ranging from 5-7 years as follows:

<u>Fixed Asset Type</u>	<u>Estimated useful life</u>
Lab equipment	5 years
Computers	5 years
Furniture and fixtures	7 years

Leasehold improvements are amortized over the shorter of the estimated useful life of the assets or the remaining lease term. Assets under capital leases are recorded in property and equipment, net on the balance sheets and depreciated in a manner similar to other property and equipment.

Expenditures for repairs and maintenance of assets are charged to expense as incurred, while major betterments are capitalized. Upon retirement or sale, the cost and related accumulated depreciation of assets disposed of are removed from the accounts and any resulting gain or loss is included in the statements of operations.

The Company reviews long-lived assets, such as property and equipment, for impairment when events or changes in circumstances indicate the carrying amount of the assets may not be recoverable. If indicators of impairment are present, the assets are tested for recoverability by comparing the carrying amount of the assets to the related estimated future undiscounted cash flows that the assets are expected to generate. If the expected cash flows are less than the carrying value of the asset, then the asset is considered to be impaired and its carrying value is written down to fair value, based on the related estimated discounted future cash flows.

Stock-Based Compensation

The Company measures the cost of employee services received in exchange for stock-based awards based on the grant-date fair value of the award. The Company recognizes compensation expense using the straight-line method over the vesting period of the awards. The Company accounts for forfeitures as they occur.

Estimating the fair value of stock-based awards requires the input of subjective assumptions, including the estimated fair value of the Company's common stock, and, for stock options, the expected life of the options and stock price volatility. The Company uses the Black-Scholes option pricing model to value its stock option awards.

As the Company's common stock has not been publicly traded, its board of directors periodically estimated the fair value of the Company's common stock considering, among other things, contemporaneous valuations of its common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants 2013 Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. The expected life of the stock options is estimated using the

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NOTES TO FINANCIAL STATEMENTS

“simplified method,” as prescribed in SEC’s Staff Accounting Bulletin (SAB) No. 107, as the Company has no historical information from which to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock option grants. The simplified method is the midpoint between the vesting period and the contractual term of the option. For stock price volatility, the Company uses comparable public companies as a basis for its expected volatility to calculate the fair value of option grants. The risk-free rate is based on the U.S. Treasury yield curve commensurate with the expected life of the option.

The assumptions used in estimating the fair value of stock-based awards represent management’s estimate and involve inherent uncertainties and the application of management’s judgment. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards.

Grant Income and Research and Development Tax Credits

The Company recognizes grant income and Delaware research and development tax credits, which are refundable irrespective of taxable income, in other income, net in the statements of operations when it is probable that the amounts will be received and the necessary qualifying conditions, as stated in the agreements, are met.

Research and Development

Research and development costs are expensed as incurred. Research and development expenses consist principally of personnel costs, including salaries, stock-based compensation, and benefits of employees, and other operational costs related to the Company’s research and development activities, including allocated facility-related expenses and external costs of outside vendors, such as clinical research organizations and clinical manufacturing organizations, and other direct and indirect costs.

Management makes estimates of the Company’s accrued research and development expenses as of each balance sheet date in the Company’s financial statements based on facts and circumstances known to the Company at that time. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual accordingly. Nonrefundable advance payments for goods and services, including fees for process development or manufacturing and distribution of clinical supplies that will be used in future research and development activities, are deferred and recognized as expense in the period that the related goods are consumed or services are performed.

Income Taxes

Income taxes are accounted for under the asset-and-liability method as required by FASB ASC Topic 740, *Income Taxes* (“ASC 740”). Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period corresponding to the enactment date. Under ASC 740, a valuation allowance is required when it is more likely than not all or some portion of the deferred tax assets will not be realized through generating sufficient future taxable income.

FASB ASC Subtopic 740-10, *Accounting for Uncertainty of Income Taxes*, (“ASC 740-10”) defines the criterion an individual tax position must meet for any part of the benefit of the tax position to be recognized in

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NOTES TO FINANCIAL STATEMENTS

financial statements prepared in conformity with GAAP. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not such tax position will be sustained on examination by the taxing authorities, based solely on the technical merits of the respective tax position. The tax benefits recognized in the financial statements from such a tax position should be measured based on the largest benefit having a greater than 50% likelihood of being realized upon ultimate settlement with the tax authority. In accordance with the disclosure requirements of ASC 740-10, the Company's policy on income statement classification of interest and penalties related to income tax obligations is to include such items as part of total interest expense and other expense, respectively.

Net Loss Per Share and Unaudited Pro Forma Net Loss Per Share

Basic net loss per share of common stock is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during each period. The weighted-average number of shares of common stock outstanding used in the basic net loss per share calculation does not include unvested restricted stock awards as these instruments are considered contingently issuable shares until they vest. Diluted net loss per share of common stock includes the effect, if any, from the potential exercise or conversion of securities, such as convertible preferred stock and stock options, which would result in the issuance of incremental shares of common stock. For diluted net loss per share, the weighted-average number of shares of common stock is the same for basic net loss per share due to the fact that when a net loss exists, dilutive securities are not included in the calculation as the impact is anti-dilutive. The Company's convertible preferred stock and unvested restricted stock entitles the holder to participate in dividends and earnings of the Company, and, if the Company were to recognize net income, it would have to use the two-class method to calculate earnings per share. The two-class method is not applicable during periods with a net loss, as the holders of the convertible preferred stock and unvested restricted stock have no obligation to fund losses.

The following potentially dilutive securities have been excluded from the computation of diluted weighted-average shares of common stock outstanding, as they would be anti-dilutive:

	December 31,	
	2018	2019
Series A convertible preferred stock	11,736,119	11,736,119
Series B convertible preferred stock	—	7,628,846
Unvested restricted stock awards	856,438	1,335,349
Stock options	588,961	2,269,742
	<u>13,181,518</u>	<u>22,970,056</u>

Amounts in the above table reflect the common stock equivalents.

The unaudited pro forma net loss per share is computed using the weighted average number of shares of common stock outstanding after giving effect to the automatic conversion of all convertible preferred stock, inclusive of the 7,628,846 shares of Series B convertible preferred stock issued in March 2020 and the 3,443,612 shares of Series C convertible preferred stock issued in August 2020, into shares of common stock upon the closing of a qualified initial public offering, as if the qualified initial public offering had occurred at the beginning of the period.

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NOTES TO FINANCIAL STATEMENTS

The following table summarizes the calculation of unaudited pro forma basic and diluted net loss per share of common stock for the year ended December 31, 2019:

(in thousands, except share and per share data)

Numerator:	
Net loss	\$ (27,570)
Denominator:	
Weighted average shares of common stock outstanding	1,668,549
Conversion of convertible preferred stock	30,437,423
Shares issued in computing unaudited pro forma weighted average basic and diluted shares of common stock outstanding	32,105,972
Pro forma net loss per common share, basic and diluted	\$ (0.86)

Recently Issued Accounting Pronouncements

Emerging Growth Company Status

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the “JOBS Act”). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act, until such time as those standards apply to private companies. The Company has elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. As a result, these financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, which requires a lessee to record a right-of-use asset and a corresponding lease liability on the balance sheet for all leases with terms longer than 12 months. A modified retrospective transition approach is required for lessees for capital and operating leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements, with certain practical expedients available. The standard is effective for the Company beginning January 1, 2022, with early adoption permitted. The Company is currently evaluating the expected impact that the standard will have on its financial statements and related disclosures.

In June 2018, the FASB issued ASU 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), as part of an initiative to reduce the cost and complexity in financial reporting and improve the usefulness of the information provided related to stock-based payment transaction for acquiring goods and services from nonemployees. Under ASU 2018-07, the guidance under ASC 505-50, *Equity-Based Payments to Non-Employees* is superseded as ASC 718 is expanded to include awards to nonemployees. In general, companies will no longer be required to remeasure (i.e., mark-to-market) the fair value of awards granted to nonemployees at each reporting date until the awards vest (the date the vesting condition is achieved). Instead, grants to nonemployees will be valued and accounted for much in the same way as awards to employees, including the ability to use the simplified method/practical expedient when determining the expected term assumption. The Company adopted ASU 2018-07 effective January 1, 2019, and the adoption did not have an impact on the Company’s financial statements.

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NOTES TO FINANCIAL STATEMENTS

In August 2018, the FASB issued ASU 2018-13, *Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurements*, which changes the fair value measurement disclosure requirements of ASC Topic 820, *Fair Value Measurement* (“ASC 820”). The goal of the ASU is to improve the effectiveness of ASC 820’s disclosure requirements. The standard is effective for fiscal years beginning after December 15, 2019 and interim periods therein. The Company is currently evaluating the potential impact of the adoption of this standard and does not anticipate that the adoption of this standard on January 1, 2020 will have a material impact the Company’s financial statements.

4. Fair Value of Financial Instruments

Fair value is the price that could be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Fair value determination in accordance with applicable accounting guidance requires that a number of significant judgments be made. Additionally, fair value is used on a nonrecurring basis to evaluate assets for impairment or as required for disclosure purposes by applicable accounting guidance on disclosures about fair value of financial instruments. Depending on the nature of the assets and liabilities, various valuation techniques and assumptions are used when estimating fair value. The Company follows the provisions of ASC 820, for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements be classified and disclosed in one of the following three categories:

- *Level 1*: Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities.
- *Level 2*: Quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liabilities.
- *Level 3*: Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

The following fair value hierarchy table presents information about the Company’s assets and liabilities measured at fair value on a recurring basis:

	Fair value measurement at reporting date using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
<i>(in thousands)</i>			
December 31, 2018:			
Assets:			
Cash equivalents (Money Market Funds)	\$ 15,400	\$ —	\$ —
December 31, 2019:			
Assets:			
Cash equivalents (Money Market Funds)	\$ 18,779	\$ —	\$ —

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PRELUDE THERAPEUTICS INCORPORATED

NOTES TO FINANCIAL STATEMENTS

5. Property and Equipment

Property and equipment consisted of the following:

	December 31,	
	2018	2019
	(in thousands)	
Lab equipment	\$ 674	\$1,842
Leasehold improvements	312	312
Computers	13	10
Furniture and fixtures	3	39
	<u>1,002</u>	<u>2,203</u>
Less accumulated depreciation	(191)	(556)
Property and equipment, net	<u>\$ 811</u>	<u>\$1,647</u>

Depreciation and amortization expense was \$0.1 million and \$0.4 million for the years ended December 31, 2018 and 2019, respectively.

In September 2019, the Company signed a 12-month capital lease for \$0.4 million of lab equipment with an effective interest rate of 9.67%. At December 31, 2019, the Company had \$0.1 million of accumulated amortization related to the capital lease. At December 31, 2019, the Company owed \$0.3 million in future minimum lease payments under the capital lease that are expected to be paid in 2020.

6. Accrued Expenses

Accrued expenses consisted of the following:

	December 31,	
	2018	2019
	(in thousands)	
Compensation and related benefits	\$ 873	\$1,631
Research and development	153	658
Other	59	314
	<u>\$1,085</u>	<u>\$2,603</u>

7. Commitments

Operating Leases

The Company leases office and laboratory space in Wilmington, Delaware under two separate noncancelable leases, which expire in November 2020 and March 2021, respectively. The Company has an option to renew both leases for additional 1-year and 6-months periods, respectively. The leases are classified as operating leases and the Company recognizes rent expense on a straight-line basis over the lease terms. The Company recognized rent expense of \$0.7 and \$0.9 million during the years ended December 31, 2018 and 2019, respectively, related to these leases.

The future minimum lease payments under the Company's operating lease agreements as of December 31, 2019 are \$1.0 million for 2020 and \$21,000 for 2021, with no commitments thereafter. In June 2020, the Company extended the lease that was set to expire in November 2020 until December 2021.

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Employment Agreements

The Company entered into employment agreements with key personnel providing for compensation and severance in certain circumstances, as defined in the respective employment agreements.

Other Research and Development Arrangements

The Company enters into agreements with contract research organizations (“CROs”) to assist in the performance of research and development activities. Expenditures to CROs will represent a significant cost in clinical development for the Company.

8. Convertible Preferred Stock and Common Stock

Convertible Preferred Stock

In August 2018, the Company issued an aggregate of 5,728,376 shares of Series A convertible preferred stock (“Series A”) for \$3.1423 per share for aggregate net proceeds of \$17.9 million.

In May 2019, the Company issued an aggregate of 7,628,846 shares of Series B convertible preferred stock (“Series B”) to existing investors at \$3.9325 per share for aggregate net proceeds of \$29.8 million.

The following is a summary of the rights, preferences, and terms of the Series A and Series B (collectively, “Convertible Preferred Stock”):

Dividends

The holders of the Convertible Preferred Stock are also entitled to receive dividends payable when, as and if declared by the Board of Directors of the Company, with the holders of common stock, paid out of any assets or on the common stock of the Company, on an as-converted to common stock basis. Dividends are non-cumulative and no dividends on common stock were declared or paid from inception through December 31, 2019.

Voting

Holders of the Convertible Preferred Stock are entitled to one vote for each share of common stock into which their shares may be converted and, subject to certain Convertible Preferred Stock class votes specified in the Company’s certificate of incorporation or as required by law, holders of the Convertible Preferred Stock and common stock vote together on an as-converted basis.

Liquidation Preference

In the event of a liquidation, dissolution or winding up of the Company, either voluntary or involuntary, or in the event of a deemed liquidation event, which includes a sale of the Company as defined in the Company’s articles of incorporation, holders of the Convertible Preferred Stock are entitled to receive, in preference to all other stockholders, an amount equal to the greater of their original investment amount plus any declared but unpaid dividends or the fair value of the common stock on a fully converted basis prior to the deemed liquidation event. If, upon the occurrence of such event, the assets and funds available for distribution are insufficient to pay such holders the full amount to which they are entitled, then the entire assets and funds legally available for distribution shall be distributed ratably among the holders of the Convertible Preferred Stock in proportion to the full amounts to which they would otherwise be entitled.

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Conversion

Each share of Convertible Preferred Stock is convertible into one share of common stock at any time at the option of the holder at a conversion price then in effect. As of December 31, 2019, the conversion price of the Series A is \$3.1423 per share and the conversion price of the Series B is \$3.9325 per share. All outstanding Convertible Preferred Stock will automatically convert into common stock at the conversion price then in effect upon (i) a qualified initial public offering of common stock with a public offering price of at least \$11.80 per share and aggregate gross proceeds of at least \$50.0 million or (ii) the affirmative election of 66% of the holders of the outstanding shares of Convertible Preferred Stock.

Redemption

The Convertible Preferred Stock is subject to redemption under certain deemed liquidation events not solely within the control of the Company, as defined, and as such is considered contingently redeemable for accounting purposes and is classified as temporary equity in the Company's balance sheets.

Future Tranche Right Feature

Pursuant to the October 2017 Series A Stock Purchase Agreement, the Series A investors could elect to purchase up to an aggregate of 5,728,376 additional shares of the Company's Series A at a fixed purchase price of \$3.1423 per share (the "Series A Future Tranche Right"). Additionally, upon the successful filing of an investigational new drug application ("IND"), the Series A investors were obligated to purchase the additional shares of Series A. In the event the holders did not purchase additional shares of Series A, their initial shares of Series A would have automatically converted into shares of the Company's common stock at a conversion ratio of 10 shares of Series A for 1 share of common stock. In August 2018, the Series A Future Tranche Right was exercised in full by the Series A investors.

Pursuant to the May 2019 Series B Stock Purchase Agreement, the Series B investors could elect to purchase an aggregate of 7,628,846 additional shares of the Company's Series B at a fixed purchase price of \$3.9325 per share (the "Series B Future Tranche Right"). Additionally, upon the successful demonstration of certain pharmacokinetic and safety profile milestones by the Company, the holders were obligated to purchase the additional shares of Series B. In the event the holders did not purchase additional shares of Series B, their initial shares of Series B would have automatically converted into shares of the Company's common stock at a conversion ratio of 10 shares of Series B for 1 share of common stock.

The Company determined that the Series A Future Tranche Right and Series B Future Tranche Right (Collectively, "Future Tranche Rights") did not meet the definition of a freestanding financial instrument as they were not legally detachable. The Future Tranche Rights were also evaluated as an embedded derivative and the Company determined they did not meet the definition of a derivative instrument for which bifurcation would be required. In March 2020, the Series B Future Tranche Right was exercised in full by the Series B investors (Note 11).

Common Stock

The holders of the common stock are entitled to one vote for each share of common stock held at all meetings of stockholders. Unless required by law, there shall be no cumulative voting. In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company, after the payment of all preferential amounts required to be paid to the holders of shares of Convertible Preferred Stock, the remaining

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funds and assets available for distribution to the stockholders of the Company will be distributed among the holders of shares of common stock, pro rata based on the number of shares of common stock held by each such holder.

9. Stock-Based Compensation

Under the Prelude Therapeutics Incorporated 2016 Stock Incentive Plan, as amended (the “Plan”), the Company may grant stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance stock awards and other forms of equity compensation to Company employees, directors and consultants. As of December 31, 2019, there were 364,853 shares of common stock available for issuance under the Plan. The Company’s stock options vest based on the terms in each award agreement, generally over four-year periods with 25% of options vesting after 1 year and then monthly thereafter, and have a term of ten years.

The Company measures stock-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards. The Company recorded stock-based compensation expense in the following expense categories in its accompanying statements of operations:

	Year Ended December 31,	
	2018	2019
	(in thousands)	
Research and development	\$ 178	\$ 437
General and administrative	2	409
	\$ 180	\$ 846

Stock Options

The following table summarizes stock option activity for the Plan in the years indicated:

	Number of shares	Weighted average exercise price per share	Weighted average remaining contractual term (years)
Outstanding at January 1, 2018	25,938	\$ 0.31	9.14
Granted	563,023	\$ 1.15	
Outstanding at December 31, 2018	588,961	\$ 1.11	9.35
Granted	1,703,692	\$ 1.84	
Forfeited	(19,669)	\$ 1.16	
Exercised	(3,242)	\$ 1.02	
Outstanding at December 31, 2019	2,269,742	\$ 1.66	9.20
Exercisable at December 31, 2019	245,794	\$ 1.04	8.24

At December 31, 2019, the aggregate intrinsic value of outstanding options and exercisable options was \$0.5 million and \$0.2 million, respectively.

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The following table summarizes information about stock options outstanding at December 31, 2019 under the Plan:

Range of Exercise Prices	Options Outstanding			Options Exercisable	
	Number Outstanding	Weighted Average Remaining Contractual Life (in years)	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
\$0.31—\$1.02	396,590	8.13	\$ 0.97	189,233	\$ 0.92
\$1.43—\$1.89	1,873,152	9.43	1.81	56,561	1.43
	<u>2,269,742</u>			<u>245,794</u>	

The weighted-average grant date fair value of options granted was \$0.86 and \$1.41 per share for the years ended December 31, 2018 and 2019, respectively. The aggregate intrinsic value of options exercised was \$3,000 for the year ended December 31, 2019. The Company recorded stock-based compensation expense of \$70,000 and \$0.4 million for the years ended December 31, 2018 and 2019, respectively, related to stock options. As of December 31, 2019, the total unrecognized compensation expense related to unvested stock option awards was \$2.3 million, which the Company expects to recognize over a weighted-average period of 3.47 years.

The fair value of each option was estimated on the date of grant using the weighted average assumptions in the table below:

	Year Ended December 31,	
	2018	2019
Expected volatility	87.01%	91.60%
Risk-free interest rate	2.85%	1.87%
Expected life (in years)	6.25	6.25
Expected dividend yield	—	—
Fair value of common stock	\$ 1.15	\$ 1.84

Restricted Stock Awards

The Company issues restricted stock awards (“RSA”) to employees that generally vest over a four-year period with 25% of awards vesting after 1 year and then monthly thereafter. Any unvested shares will be forfeited upon termination of services. The fair value of an RSA is equal to the fair market value price of the Company’s common stock on the date of grant. RSA expense is amortized straight-line over the vesting period.

The following table summarizes activity related to RSA stock-based payment awards:

	Number of shares	Weighted-average grant date fair value
Unvested balance at January 1, 2019	856,438	\$ 0.74
Granted	778,141	1.89
Vested	(299,230)	0.68
Unvested balance at December 31, 2019	<u>1,335,349</u>	\$ 1.42

The Company recorded stock-based compensation expense of \$0.1 million and \$0.4 million for the years ended December 31, 2018 and 2019, respectively, related to RSAs. As of December 31, 2019, the total

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unrecognized expense related to all RSAs was \$1.6 million, which the Company expects to recognize over a weighted-average period of 3.14 years.

10. Income Taxes

The tax effects of temporary differences that gave rise to significant portions of the deferred tax assets and liabilities were as follows:

(in thousands)	December 31,	
	2018	2019
Deferred tax assets:		
Net operating loss carryforwards	\$ 5,461	\$ 13,659
Research and development credits	739	2,216
Gross deferred tax assets	6,200	15,875
Less: valuation allowance	(6,164)	(15,409)
Total deferred tax asset	36	466
Deferred tax liability		
Stock-based compensation	—	(399)
Depreciation	(36)	(67)
Total deferred tax liabilities	(36)	(466)
	<u>\$ —</u>	<u>\$ —</u>

In assessing the need for a valuation allowance, management must determine that there will be sufficient taxable income to allow for the realization of deferred tax assets. Based upon the historical and anticipated future losses, management has determined that the deferred tax assets do not meet the more likely than not threshold for realizability. Accordingly, a full valuation allowance has been recorded against the Company's net deferred tax assets as of December 31, 2018 and 2019. The valuation allowance increased by \$4.6 million and \$9.2 million during the years ended December 31, 2018 and 2019, respectively.

A reconciliation of the federal income tax rate to the Company's effective tax rate is as follows:

	Year ended December 31,	
	2018	2019
Federal tax benefit at statutory rate	(21.0)%	(21.0)%
State tax, net of federal benefit	(6.9)	(6.9)
Return to provision	—	(0.7)
Permanent differences	1.4	0.4
Research and development	(5.0)	(5.4)
Change in valuation allowance	31.5	33.6
	<u>—%</u>	<u>—%</u>

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The following table summarizes carryforwards of federal, state and local net operating losses (“NOL”) and research tax credits:

(in thousands)	December 31,	
	2018	2019
NOL carryforwards—Federal	\$ 20,298	\$ 49,005
NOL carryforwards—State	20,298	49,005
Research tax credits—Federal	706	2,182
Research tax credits—State	43	43

The NOL carryforwards begin expiring in 2036 for federal and Delaware state income tax purposes, however; all federal and Delaware state NOL carryforwards generated subsequent to January 1, 2018, are able to be carried forward indefinitely. As of December 31, 2019, the Company also had federal and Delaware research and development tax credit carryforwards of \$2.2 million and \$43,000, respectively that will begin to expire in 2036, unless previously utilized.

The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. To date, the Company has not performed an analysis to determine whether or not ownership changes have occurred since inception. Delaware state NOLs may also be limited.

As of December 31, 2019, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company’s statement of operations. Due to NOL and tax credit carry forwards that remain unutilized, income tax returns for tax years from 2016, 2017 and 2018 remain subject to examination by the taxing jurisdictions. The NOL carryforwards remain subject to review until utilized.

11. Subsequent Events

In preparing the financial statements as of and for the year ended December 31, 2019, the Company evaluated subsequent events for recognition and measurement purposes through July 23, 2020, the date the financial statements were originally issued, and through September 21, 2020, the date the revised financial statements were issued.

Equity Transactions

In March 2020, the Company’s Series B investors exercised their Future Tranche Right and purchased 7,628,846 shares of Series B for net proceeds of approximately \$29.9 million.

In August 2020, the Company’s existing Convertible Preferred Stock investors as well as a new investor purchased 3,443,612 shares of Series C convertible preferred stock at a price of \$14.5197 per share for net proceeds of approximately \$49.9 million.

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Reverse Stock Split

In September 2020, the Company effected a one-for-1.1566 reverse stock split of its common stock and convertible preferred stock. No fractional shares were issued in connection with the reverse stock split. Any fractional share resulting from the reverse stock split was rounded down to the nearest whole share, and in lieu of any fractional shares, the Company will pay in cash to the holders of such fractional shares an amount equal to the fair value, as determined by the board of directors, of such fractional shares. All common stock, convertible preferred stock, per share and related information presented in the financial statements and accompanying notes have been retroactively adjusted to reflect the reverse stock split.

Increase in Authorized Shares of Common Stock and Preferred Stock; Creation of Non-Voting Common Stock

In August 2020, the Company effected an increase in the number of authorized shares of its common stock from 42,000,000 shares to 58,850,259 shares, including 12,850,259 shares of the common stock that are non-voting and are designated as “non-voting common stock,” with the remaining 46,000,000 shares of the common stock designated as “voting common stock,” and effected an increase in the number of authorized shares of its Convertible Preferred Stock from 32,074,008 shares to 35,221,066 shares, of which 4,000,000 shares were designated as Series C. In September 2020, the Company approved another increase in the number of authorized voting common stock, to be effective immediately prior to the completion of the Company’s IPO, from 46,000,000 shares to 487,149,741 shares.

The holders of the voting common stock are entitled to one vote for each share of voting common stock held at all meetings of stockholders. Except as otherwise required by law, the holders of non-voting common stock shall not be entitled to vote at any meetings of stockholders (or written actions in lieu of meetings) and the shares of non-voting common stock shall not be included in determining the number of shares voting or entitled to vote on any matter. Unless required by law, there shall be no cumulative voting. Any holder of non-voting common stock may elect to convert each share of non-voting common stock into one fully paid and non-assessable share of voting common stock at any time by providing written notice to the Company; provided, however, that such shares of non-voting common stock may only be converted by each investors into shares of voting common stock during such time or times as immediately prior to or as a result of such conversion would not result in the holder(s) thereof being a beneficial owner (for purposes of Section 13(d) of the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

Coronavirus Pandemic

On March 10, 2020, the World Health Organization characterized the novel COVID-19 virus as a global pandemic. There is significant uncertainty as to the likely effects of this disease which may, among other things, materially impact the Company’s planned clinical trials. This pandemic or outbreak could result in difficulty securing clinical trial site locations, CROs, and/or trial monitors and other critical vendors and consultants supporting the trial. In addition, outbreaks or the perception of an outbreak near a clinical trial site location could impact the Company’s ability to enroll patients. These situations, or others associated with COVID-19, could cause delays in the Company’s clinical trial plans and could increase expected costs, all of which could have a material adverse effect on the Company’s business and its financial condition. At the current time, the Company is unable to quantify the potential effects of this pandemic on its future financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

**BALANCE SHEETS
(UNAUDITED)**

(in thousands, except share data)	December 31, 2019	September 30, 2020
Assets		
Current assets:		
Cash and cash equivalents	\$ 18,879	\$ 234,792
Prepaid expenses and other current assets	1,345	3,269
Total current assets	20,224	238,061
Property and equipment, net	1,647	1,620
Total assets	<u>\$ 21,871</u>	<u>\$ 239,681</u>
Liabilities, convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Capital lease obligation	\$ 258	\$ —
Accounts payable	1,974	5,074
Accrued expenses and other current liabilities	2,603	6,285
Total current liabilities	4,835	11,359
Other liabilities	5	15
Total liabilities	<u>4,840</u>	<u>11,374</u>
Convertible preferred stock, \$0.0001 par value:		
Series A convertible preferred stock: 13,574,008 shares and no shares authorized at December 31, 2019 and September 30, 2020, respectively; 11,736,119 shares and no shares issued and outstanding at December 31, 2019 and September 30, 2020, respectively	36,595	—
Series B convertible preferred stock: 18,500,000 shares and no shares authorized at December 31, 2019 and September 30, 2020; 7,628,846 shares and no shares issued and outstanding at December 31, 2019 and September 30, 2020, respectively	29,848	—
Series C convertible preferred stock: no shares authorized, issued or outstanding at December 31, 2019 and September 30, 2020	—	—
Total convertible preferred stock	<u>66,443</u>	<u>—</u>
Commitments		
Stockholders' equity (deficit):		
Voting common stock, \$0.0001 par value: 42,000,000 and 487,149,741 shares authorized at December 31, 2019 and September 30, 2020, respectively; 3,161,653 and 32,593,010 shares issued and outstanding at December 31, 2019 and September 30, 2020, respectively	—	3
Non-voting common stock, \$0.0001 par value; No shares and 12,850,259 shares authorized at December 31, 2019 and September 30, 2020, respectively; No shares and 11,110,371 shares issued and outstanding at December 31, 2019 and September 30, 2020, respectively	—	1
Additional paid-in capital	1,085	316,479
Accumulated deficit	(50,497)	(88,176)
Total stockholders' equity (deficit)	<u>(49,412)</u>	<u>228,307</u>
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	<u>\$ 21,871</u>	<u>\$ 239,681</u>

See accompanying notes to unaudited interim financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

**STATEMENTS OF OPERATIONS
(UNAUDITED)**

(in thousands, except share and per share data)	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2020	2019	2020
Operating expenses:				
Research and development	\$ 5,490	\$ 15,293	\$ 15,430	\$ 33,605
General and administrative	1,394	2,851	2,584	5,712
Total operating expenses	6,884	18,144	18,014	39,317
Loss from operations	(6,884)	(18,144)	(18,014)	(39,317)
Other income, net	150	1,384	483	1,638
Net loss	\$ (6,734)	\$ (16,760)	\$ (17,531)	\$ (37,679)
Per share information:				
Net loss per share of common stock, basic and diluted	\$ (3.93)	\$ (5.25)	\$ (10.80)	\$ (15.83)
Weighted average common shares outstanding, basic and diluted	1,713,371	3,194,471	1,622,546	2,380,100

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PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF CHANGES IN CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT) (UNAUDITED)

(in thousands, except shares)	Convertible preferred stock				Stockholders' deficit				
	Series A		Series B		Common stock		Additional paid-in capital	Accumulated deficit	Total
	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at January 1, 2019	11,736,119	\$ 36,595	—	\$ —	2,380,270	\$ —	\$ 234	\$ (22,927)	\$ (22,693)
Stock-based compensation expense	—	—	—	—	—	—	82	—	82
Net loss	—	—	—	—	—	—	—	(5,241)	(5,241)
Balance at March 31, 2019	<u>11,736,119</u>	<u>36,595</u>	<u>—</u>	<u>—</u>	<u>2,380,270</u>	<u>—</u>	<u>316</u>	<u>(28,168)</u>	<u>(27,852)</u>
Exercise of stock options	—	—	—	—	3,242	—	5	—	5
Sale of Series B convertible preferred stock, net of issuance costs of \$152	—	—	7,628,846	29,848	—	—	—	—	—
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	345,840	—	141	—	141
Net loss	—	—	—	—	—	—	—	(5,556)	(5,556)
Balance at June 30, 2019	<u>11,736,119</u>	<u>36,595</u>	<u>7,628,846</u>	<u>29,848</u>	<u>2,729,352</u>	<u>—</u>	<u>462</u>	<u>(33,724)</u>	<u>(33,262)</u>
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	432,301	—	297	—	297
Net loss	—	—	—	—	—	—	—	(6,734)	(6,734)
Balance at September 30, 2019	<u>11,736,119</u>	<u>\$ 36,595</u>	<u>7,628,846</u>	<u>\$ 29,848</u>	<u>3,161,653</u>	<u>\$ —</u>	<u>\$ 759</u>	<u>\$ (40,458)</u>	<u>\$ (39,699)</u>

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(in thousands, except shares)	Convertible preferred stock						Stockholders' equity (deficit)						
	Series A		Series B		Series C		Voting common stock		Non-voting common stock		Additional paid-in	Accumulated	Total
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	capital	deficit	
Balance at													
January 1, 2020	11,736,119	\$ 36,595	7,628,846	\$ 29,848	—	\$ —	3,161,653	\$ —	—	\$ —	\$ 1,085	\$ (50,497)	\$ (49,412)
Sale of Series B convertible preferred stock, net of issuance costs of \$58	—	—	7,628,846	29,942	—	—	—	—	—	—	—	—	—
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	—	—	432,301	—	—	—	362	—	362
Net loss	—	—	—	—	—	—	—	—	—	—	—	(9,511)	(9,511)
Balance at													
March 31, 2020	<u>11,736,119</u>	<u>36,595</u>	<u>15,257,692</u>	<u>59,790</u>	<u>—</u>	<u>—</u>	<u>3,593,954</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>1,447</u>	<u>(60,008)</u>	<u>(58,561)</u>
Exercise of stock options	—	—	—	—	—	—	36,745	—	—	—	31	—	31
Stock-based compensation expense	—	—	—	—	—	—	—	—	—	—	627	—	627
Net loss	—	—	—	—	—	—	—	—	—	—	—	(11,408)	(11,408)
Balance at June 30, 2020	<u>11,736,119</u>	<u>36,595</u>	<u>15,257,692</u>	<u>59,790</u>	<u>—</u>	<u>—</u>	<u>3,630,699</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>2,105</u>	<u>(71,416)</u>	<u>(69,311)</u>
Exercise of stock options	—	—	—	—	—	—	61,509	—	—	—	65	—	65
Sale of Series C convertible preferred stock, net of issuance costs of \$174	—	—	—	—	3,443,612	49,826	—	—	—	—	—	—	—
Conversion of convertible preferred stock into voting and non-voting common stock upon initial public offering	(11,736,119)	(36,595)	(15,257,692)	(59,790)	(3,443,612)	(49,826)	19,327,052	2	11,110,371	1	146,208	—	146,211
Sale of common stock in initial public offering, net of offering costs of \$2,538	—	—	—	—	—	—	9,573,750	1	—	—	166,629	—	166,630
Stock-based compensation expense	—	—	—	—	—	—	—	—	—	—	1,472	—	1,472
Net loss	—	—	—	—	—	—	—	—	—	—	—	(16,760)	(16,760)
Balance at													
September 30, 2020	<u>—</u>	<u>\$ —</u>	<u>—</u>	<u>\$ —</u>	<u>—</u>	<u>\$ —</u>	<u>32,593,010</u>	<u>\$ 3</u>	<u>11,110,371</u>	<u>\$ 1</u>	<u>\$ 316,479</u>	<u>\$ (88,176)</u>	<u>\$ 228,307</u>

See accompanying notes to unaudited interim financial statements.

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Pursuant To 17 C.F.R. Section 200.83**

PRELUDE THERAPEUTICS INCORPORATED

**STATEMENTS OF CASH FLOWS
(UNAUDITED)**

(in thousands)	Nine months ended September 30,	
	2019	2020
Cash flows used in operating activities:		
Net loss	\$(17,531)	\$(37,679)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	254	409
Stock-based compensation	520	2,461
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(344)	(1,924)
Accounts payable	(76)	1,931
Accrued expenses and other liabilities	(19)	3,472
Net cash used in operating activities	<u>(17,196)</u>	<u>(31,330)</u>
Cash flows used in investing activities:		
Purchases of property and equipment	(581)	(292)
Net cash used in investing activities	<u>(581)</u>	<u>(292)</u>
Cash flows provided by financing activities:		
Proceeds from the issuance of common stock upon initial public offering, net of offering costs	—	167,929
Proceeds from the sale of Series C convertible preferred stock, net of offering costs	—	49,826
Proceeds from the sale of Series B convertible preferred stock, net of offering costs	29,848	29,942
Payment of capital lease obligation	(31)	(258)
Proceeds from the exercise of stock options	5	96
Net cash provided by financing activities	<u>29,822</u>	<u>247,535</u>
Net increase in cash and cash equivalents	12,045	215,913
Cash and cash equivalents at beginning of period	15,595	18,879
Cash and cash equivalents at end of period	<u>\$ 27,640</u>	<u>\$ 234,792</u>
Supplemental disclosures:		
Property and equipment in accounts payable	<u>\$ 108</u>	<u>\$ 90</u>
Offering costs in accrued expenses and other current liabilities	<u>\$ —</u>	<u>\$ 220</u>
Offering costs in accounts payable	<u>\$ —</u>	<u>\$ 1,079</u>

See accompanying notes to unaudited interim financial statements.

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PRELUDE THERAPEUTICS INCORPORATED

NOTES TO UNAUDITED INTERIM FINANCIAL STATEMENTS

1. Background

Prelude Therapeutics Incorporated (the “Company”) was incorporated in Delaware on February 5, 2016 and is a clinical-stage precision oncology company focused on discovering and developing small molecule therapies optimized to target the key driver mechanisms in cancers with high unmet need. Since beginning operations, the Company has devoted substantially all its efforts to research and development, conducting preclinical and clinical studies, recruiting management and technical staff, administration, and raising capital.

In September 2020, the Company closed its initial public offering (“IPO”) in which the Company issued and sold 9,573,750 shares of its common stock at a public offering price of \$19.00 per share for net proceeds of \$166.6 million after deducting underwriting discounts, commissions and other offering expenses paid or to be paid. Subsequent to the closing of the IPO, there were no shares of convertible preferred stock outstanding. In connection with the closing of the IPO, the Company amended and restated its Fifth Amended and Restated Certificate of Incorporation to change the authorized capital stock to 500,000,000 shares designated as common stock (of which 12,850,259 shares are non-voting common stock) and 10,000,000 shares designated as preferred stock, all with a par value of \$0.0001 per share.

2. Risks and liquidity

The Company is subject to a number of risks common to early-stage companies in the biotechnology industry. Principal among these risks are the uncertainties in the development process, development of the same or similar technological innovations by competitors, protection of proprietary technology, dependence on key personnel, compliance with government regulations and approval requirements, and the need to obtain additional financing to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive pre-clinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure, and extensive compliance-reporting capabilities. There can be no assurance that the Company’s research and development will be successfully completed, that adequate protection for the Company’s technology will be obtained, that any products developed will obtain necessary government regulatory approval, or that any approved products will be commercially viable. The Company operates in an environment of rapid change in technology and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and contractors.

Since its inception, the Company has incurred operating losses and has an accumulated deficit of \$88.2 million at September 30, 2020. The Company has no revenue to date and devotes its efforts to research and development. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates currently in development.

The Company believes that its cash and cash equivalents as of September 30, 2020, which includes the net proceeds of approximately \$166.6 million from the IPO of the Company’s common stock completed in September 2020, will be sufficient to fund its operating expenses and capital expenditure requirements into the second half of 2022.

To fund its operating expenses and capital expenditure requirements after that date, the Company plans to seek additional funding through public or private equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into strategic alliances or other arrangements on favorable terms, or at all. The terms of any financing may adversely affect the holdings or the rights of the Company’s

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stockholders. If the Company is unable to obtain funding, the Company could be required to delay, reduce or eliminate research and development programs, product portfolio expansion or future commercialization efforts, which could adversely affect its business prospects.

On March 10, 2020, the World Health Organization characterized the novel COVID-19 virus as a global pandemic. There is significant uncertainty as to the likely effects of this disease which may, among other things, materially impact the Company's planned clinical trials. This pandemic or outbreak could result in difficulty securing clinical trial site locations, CROs, and/or trial monitors and other critical vendors and consultants supporting the trial. In addition, outbreaks or the perception of an outbreak near a clinical trial site location could impact the Company's ability to enroll patients. These situations, or others associated with COVID-19, could cause delays in the Company's clinical trial plans and could increase expected costs, all of which could have a material adverse effect on the Company's business and its financial condition. At the current time, the Company is unable to quantify the potential effects of this pandemic on its future financial statements.

3. Summary of significant accounting policies

The summary of significant accounting policies included in the Company's financial statements for the year ended December 31, 2019 can be found in "Note 3. Summary of significant accounting policies" of the Company's prospectus filed with the Securities and Exchange Commission (the "SEC") on September 25, 2020 (the "Prospectus"). Those policies have not materially changed, except as set forth below.

Basis of presentation

The accompanying unaudited interim financial statements have been prepared in accordance with generally accepted accounting principles ("GAAP") for interim financial information, the instructions to Form 10-Q and Article 10 of Regulation S-X. They do not include all of the information and notes required by GAAP for complete financial statements. In the opinion of management, all adjustments (consisting of normal recurring accruals) considered necessary for a fair presentation have been included. Operating results for the three and nine month periods ended September 30, 2020 are not necessarily indicative of the results that may be expected for the year ended December 31, 2020. The accompanying unaudited interim financial statements should be read in conjunction with the annual audited financial statements and related notes as of and for the year ended December 31, 2019 found in the Prospectus filed with the SEC on September 25, 2020. Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

On September 18, 2020, the Company's board of directors and stockholders approved a 1.1566-to-one reverse stock split of the Company's issued and outstanding shares of common stock and convertible preferred stock. All share and per share amounts in the unaudited interim financial statements and notes hereto have been retrospectively adjusted for all periods presented to give effect to the reverse stock split.

The completion of the IPO, as described above, impacts the comparability of certain amounts to the corresponding prior year period, including earnings per share.

Use of estimates

The preparation of the unaudited interim financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and contingent liabilities at the date of the unaudited interim financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

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Estimates and assumptions are periodically reviewed and the effects of the revisions are reflected in the accompanying unaudited interim financial statements in the period they are determined to be necessary. Prior to the IPO, significant areas that required management's estimates included the fair value of the Company's common stock, stock-based compensation assumptions and accrued clinical trial expenses. Subsequent to the IPO, the most significant estimate relates to accrued clinical trial expenses.

Income taxes

Based upon the historical and anticipated future losses, management has determined that the deferred tax assets generated by net operating losses and research and development credits do not meet the more likely than not threshold for realizability. Accordingly, a full valuation allowance has been recorded against the Company's net deferred tax assets as of December 31, 2019 and September 30, 2020.

Net Loss Per Share

Basic net loss per share of common stock is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during each period. The weighted-average number of shares of common stock outstanding used in the basic net loss per share calculation does not include unvested restricted stock awards as these instruments are considered contingently issuable shares until they vest. Diluted net loss per share of common stock includes the effect, if any, from the potential exercise or conversion of securities, such as convertible preferred stock and stock options, which would result in the issuance of incremental shares of common stock. For diluted net loss per share, the weighted-average number of shares of common stock is the same for basic net loss per share due to the fact that when a net loss exists, dilutive securities are not included in the calculation as the impact is anti-dilutive. The Company's convertible preferred stock and unvested restricted stock entitles the holder to participate in dividends and earnings of the Company, and, if the Company were to recognize net income, it would have to use the two-class method to calculate earnings per share. The two-class method is not applicable during periods with a net loss, as the holders of the convertible preferred stock and unvested restricted stock have no obligation to fund losses.

The following potentially dilutive securities have been excluded from the computation of diluted weighted-average shares of common stock outstanding, as they would be anti-dilutive:

	September 30,	
	2019	2020
Series A convertible preferred stock	11,736,119	—
Series B convertible preferred stock	7,628,846	—
Unvested restricted stock awards	1,394,056	1,312,024
Stock options	2,189,333	6,649,882
	<u>22,948,354</u>	<u>7,961,906</u>

Amounts in the above table reflect the common stock equivalents.

Recently Issued Accounting Pronouncements

Emerging Growth Company Status

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). Under the JOBS Act, emerging growth companies can delay adopting new or revised

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accounting standards issued subsequent to the enactment of the JOBS Act, until such time as those standards apply to private companies. The Company has elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. As a result, these unaudited interim financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, which requires a lessee to record a right-of-use asset and a corresponding lease liability on the balance sheet for all leases with terms longer than 12 months. A modified retrospective transition approach is required for lessees for capital and operating leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements, with certain practical expedients available. The standard is effective for the Company beginning January 1, 2022, with early adoption permitted. The Company is currently evaluating the expected impact that the standard will have on its financial statements and related disclosures.

In August 2018, the FASB issued ASU 2018-13, *Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurements*, which changes the fair value measurement disclosure requirements of ASC Topic 820, *Fair Value Measurement* (“ASC 820”). The goal of the ASU is to improve the effectiveness of ASC 820’s disclosure requirements. The standard is effective for fiscal years beginning after December 15, 2019 and interim periods therein. The adoption of this standard on January 1, 2020 did not have a material impact on the Company’s unaudited interim financial statements.

4. Fair Value of Financial Instruments

Fair value is the price that could be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Fair value determination in accordance with applicable accounting guidance requires that a number of significant judgments be made. Additionally, fair value is used on a nonrecurring basis to evaluate assets for impairment or as required for disclosure purposes by applicable accounting guidance on disclosures about fair value of financial instruments. Depending on the nature of the assets and liabilities, various valuation techniques and assumptions are used when estimating fair value. The Company follows the provisions of ASC 820, for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements be classified and disclosed in one of the following three categories:

- *Level 1:* Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities.
- *Level 2:* Quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liabilities.
- *Level 3:* Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

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The following fair value hierarchy table presents information about the Company's assets and liabilities measured at fair value on a recurring basis:

(in thousands)	Fair value measurement at reporting date using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2019:			
Assets:			
Cash equivalents (Money Market Funds)	\$ 18,779	\$ —	\$ —
September 30, 2020:			
Assets:			
Cash equivalents (Money Market Funds)	\$ 233,364	\$ —	\$ —

5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

(in thousands)	December 31, 2019	September 30, 2020
Compensation and related benefits	\$ 1,631	\$ 2,099
Research and development	658	3,763
Offering costs	—	220
Professional services and other	314	203
	\$ 2,603	\$ 6,285

6. Convertible Preferred Stock and Common Stock

Preferred Stock Financings

In August 2020, the Company's existing Convertible Preferred Stock investors as well as a new investor purchased 3,443,612 shares of Series C at a price of \$14.5197 per share for net proceeds of approximately \$49.8 million.

In March 2020, the Company's Series B investors exercised their Future Tranche Right and purchased 7,628,846 shares of Series B for net proceeds of approximately \$29.9 million.

Initial Public Offering

In September 2020, the Company completed its IPO in which the Company sold 9,573,750 shares of its common stock at a public offering price of \$19.00 per share. The Company received net proceeds of \$166.6 million after deducting underwriting discounts, commissions, and other offering expenses paid by the Company. In addition, immediately prior to the closing of the IPO on September 29, 2020, (i) all of the Company's outstanding shares of convertible preferred stock converted into an aggregate of 30,437,423 shares of common stock (of which, 11,110,371 shares are non-voting common stock) and (ii) the Company filed an amended and restated certificate of incorporation to, among other things, increase the number of authorized shares of common stock to 500,000,000.

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Common Stock

The Company has two classes of common stock; “voting common stock” and “non-voting common stock.” The holders of the voting common stock are entitled to one vote for each share of voting common stock held at all meetings of stockholders. Except as otherwise required by law, the holders of non-voting common stock shall not be entitled to vote at any meetings of stockholders (or written actions in lieu of meetings) and the shares of non-voting common stock shall not be included in determining the number of shares voting or entitled to vote on any matter. Unless required by law, there shall be no cumulative voting. Any holder of non-voting common stock may elect to convert each share of non-voting common stock into one fully paid and non-assessable share of voting common stock at any time by providing written notice to the Company; provided that as a result of such conversion, such holder, together with its affiliates and any members of a Schedule 13(d) group with such holder, would not beneficially own in excess of 9.99% of the Company’s common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in the Company’s restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder of non-voting common stock upon 61 days’ notice to the Company.

7. Stock-Based Compensation

The Company has two equity incentive plans: the 2016 Equity Incentive Plan, as amended, and the 2020 Equity Incentive Plan. New awards can only be granted under the 2020 Equity Incentive Plan (the “Plan”). The total number of shares initially authorized under the Plan was 4,680,000. Of this amount, 4,677,407 shares were available for future grants as of September 30, 2020. The number of shares of the Company’s common stock that may be issued pursuant to rights granted under the Plan shall automatically increase on January 1st of each year, commencing on January 1, 2021 and continuing for ten years, in an amount equal to five percent of the total number of shares of the Company’s common stock outstanding on December 31st of the preceding calendar year, subject to the discretion of the board of directors or compensation committee to determine a lesser number of shares shall be added for such year. The Plan provides for the granting of common stock, incentive stock options, nonqualified stock options, restricted stock awards, and/or stock appreciation rights to employees, directors, and other persons, as determined by the Company’s board of directors. The Company’s stock options vest based on the terms in each award agreement, generally over four-year periods with 25% of options vesting after 1 year and then monthly thereafter, and have a term of ten years. In September 2020, the Company also adopted the 2020 Employee Stock Purchase Plan (the “ESPP”), which includes 520,000 shares of common stock reserved for future issuance. No shares have been issued from the ESPP as of September 30, 2020.

The Company measures stock-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards. The Company recorded stock-based compensation expense in the following expense categories in its accompanying statements of operations:

(in thousands)	Three Months Ended September 30,		Nine Months September 30,	
	2019	2020	2019	2020
Research and development	\$ 135	\$ 630	\$250	\$1,047
General and administrative	162	842	270	1,414
	<u>\$ 297</u>	<u>\$ 1,472</u>	<u>\$520</u>	<u>\$2,461</u>

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Stock Options

The following table summarizes stock option activity for the periods indicated:

	Number of shares	Weighted average exercise price per share	Weighted average remaining contractual term (years)
Outstanding at January 1, 2020	2,269,742	\$ 1.66	9.20
Granted	4,594,130	\$ 9.38	
Exercised	(98,254)	\$ 0.98	
Forfeited	(115,736)	\$ 1.37	
Outstanding at September 30, 2020	<u>6,649,882</u>	\$ 7.00	9.40
Exercisable at September 30, 2020	<u>783,236</u>	\$ 1.64	8.40

At September 30, 2020, the aggregate intrinsic value of outstanding options and exercisable options was \$153.7 million and \$22.3 million, respectively.

The following table summarizes information about stock options outstanding at September 30, 2020 under the Plan:

Range of Exercise Prices	Options Outstanding			Options Exercisable	
	Number Outstanding	Weighted Average Remaining Contractual Life (in years)	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
\$0.31 - \$1.02	253,931	7.43	\$ 0.98	162,037	\$ 0.96
\$1.43 - \$1.89	3,259,095	9.05	1.85	619,998	1.79
\$12.85 - \$19.00	3,136,856	9.92	12.86	1,201	12.85
	<u>6,649,882</u>			<u>783,236</u>	

The weighted-average grant date fair value of options granted was \$1.40 and \$8.44 per share for the nine months ended September 30, 2019 and 2020, respectively. The aggregate intrinsic value of options exercised was \$2.9 million for the nine months ended September 30, 2020. The Company recorded stock-based compensation expense of \$0.2 million and \$1.2 million for the three months ended September 30, 2019 and 2020, respectively, related to stock options. The Company recorded stock-based compensation expense of \$0.3 million and \$1.9 million for the nine months ended September 30, 2019 and 2020, respectively, related to stock options. As of September 30, 2020, the total unrecognized compensation expense related to unvested stock option awards was \$39.1 million, which the Company expects to recognize over a weighted-average period of 3.74 years.

The fair value of each option was estimated on the date of grant using the weighted average assumptions in the table below:

	Nine months ended September 30,	
	2019	2020
Expected volatility	91.60%	115.09%
Risk-free interest rate	1.88%	0.42%
Expected life (in years)	6.25	6.25
Expected dividend yield	—	—

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Restricted Stock Awards

The Company issues restricted stock awards (“RSA”) to employees that generally vest over a four-year period with 25% of awards vesting after one year and then monthly thereafter. Any unvested shares will be forfeited upon termination of services. The fair value of an RSA is equal to the fair market value price of the Company’s common stock on the date of grant. RSA expense is amortized straight-line over the vesting period.

The following table summarizes activity related to RSA stock-based payment awards:

	Number of shares	Weighted-average grant date fair value
Unvested balance at January 1, 2020	1,335,349	\$ 1.42
Granted	432,301	\$ 3.26
Vested	<u>(455,626)</u>	<u>\$ 1.40</u>
Unvested balance at September 30, 2020	<u>1,312,024</u>	<u>\$ 2.03</u>

The Company recorded stock-based compensation expense of \$0.1 million and \$0.3 million for the three months ended September 30, 2019 and 2020, respectively, related to RSAs. The Company recorded stock-based compensation expense of \$0.3 million and \$0.6 million for the nine months ended September 30, 2019 and 2020, respectively, related to RSAs. As of September 30, 2020, the total unrecognized expense related to all RSAs was \$2.4 million, which the Company expects to recognize over a weighted-average period of 2.94 years.

8. Subsequent Events

On November 1, 2020, the Company entered into a Second Amended and Restated Entrepreneur Client License Agreement (the “Amendment”) with Delaware Innovation Space, Inc. (“DISI”) to amend the Amended and Restated Entrepreneur Client License Agreement dated June 1, 2020 (the “Original Agreement”) relating to the Company’s office and laboratory space in Wilmington, Delaware. The Amendment provides for the expansion of the premises by approximately 8,800 rentable square feet (the “Expansion Space”). Upon inclusion of the Expansion Space, the Company will license approximately 19,800 rentable square feet of office space (the “Premises”) from DISI (the “License”). Pursuant to the Amendment, the initial term of the License is twenty-six months commencing on November 1, 2020 and terminating on December 31, 2022 (the “Initial Term”).

The total base license fee for the Premises through the Initial Term is expected to be \$3.0 million (the “License Fee”). The Company has an option to renew the License for twelve months commencing on January 1, 2023 at a monthly renewal license fee increased by 5.0% for a total of \$1.4 million payable during the renewal term.

Pursuant to the Amendment, the Company was granted a right of first offer (the “ROFO”) in connection with certain licensable additional space on the Premises that becomes vacant prior to October 31, 2021 (“Available ROFO Space”). If the Company exercises its ROFO, the Company will pay to DISI an increased monthly license fee not to exceed \$0.2 million per month at any time during the Initial Term. As consideration for the ROFO, the Company paid DISI a one-time payment of \$0.2 million.

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Shares



Prelude Therapeutics Incorporated

Common Stock

PRELIMINARY PROSPECTUS

MORGAN STANLEY

GOLDMAN SACHS & CO. LLC

BofA SECURITIES

Until _____, 2021 (25 days after the date of this prospectus), all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This delivery requirement is in addition to the dealers' obligation to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.

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PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 13. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION.

The following table sets forth all costs and expenses, other than underwriting discounts and commissions, paid or payable by the Registrant in connection with the sale of the common stock being registered. All amounts shown are estimates except for the Securities and Exchange Commission, or SEC, registration fee, the Financial Industry Regulatory Approval, or FINRA, filing fee and the Nasdaq Global Select Market listing fee:

	Amount Paid or To Be Paid
SEC registration fee	*
FINRA filing fee	*
The Nasdaq Global Select Market listing fee	*
Printing and engraving expenses	*
Legal fees and expenses	*
Accounting fees and expenses	*
Blue Sky, qualification fees and expenses	*
Transfer agent and registrar fees and expenses	*
Miscellaneous expenses	*
Total	*

* To be provided by amendment.

ITEM 14. INDEMNIFICATION OF DIRECTORS AND OFFICERS.

Section 145 of the Delaware General Corporation Law, or DGCL, authorizes a court to award, or a corporation's board of directors to grant, indemnity to directors and officers under certain circumstances and subject to certain limitations. The terms of Section 145 of the DGCL are sufficiently broad to permit indemnification under certain circumstances for liabilities, including reimbursement of expenses incurred, arising under the Securities Act of 1933, as amended, or the Securities Act.

As permitted by the DGCL, the Registrant's restated certificate of incorporation contains provisions that eliminate the personal liability of its directors for monetary damages for any breach of fiduciary duties as a director, except liability for the following:

- any breach of the director's duty of loyalty to the Registrant or its stockholders;
- acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- under Section 174 of the DGCL (regarding unlawful dividends and stock purchases); or
- any transaction from which the director derived an improper personal benefit.

As permitted by the DGCL, the Registrant's restated bylaws provide that:

- the Registrant is required to indemnify its directors and executive officers to the fullest extent permitted by the DGCL, subject to limited exceptions;
- the Registrant may indemnify its other employees and agents as set forth in the DGCL;

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- the Registrant is required to advance expenses, as incurred, to its directors and executive officers in connection with a legal proceeding to the fullest extent permitted by the DGCL, subject to limited exceptions; and
- the rights conferred in the restated bylaws are not exclusive.

The Registrant entered into indemnification agreements with each of its current directors and executive officers to provide these directors and executive officers additional contractual assurances regarding the scope of the indemnification set forth in the Registrant's restated certificate of incorporation and restated bylaws and to provide additional procedural protections. There is no pending litigation or proceeding involving a director or executive officer of the Registrant for which indemnification is sought. Reference is also made to the underwriting agreement to be filed as Exhibit 1.1 to this registration statement, which provides for the indemnification of executive officers, directors and controlling persons of the Registrant against certain liabilities. The indemnification provisions in the Registrant's restated certificate of incorporation, restated bylaws and the indemnification agreements entered into between the Registrant and each of its directors and executive officers may be sufficiently broad to permit indemnification of the Registrant's directors and executive officers for liabilities arising under the Securities Act.

The Registrant has directors' and officers' liability insurance for securities matters.

ITEM 15. RECENT SALES OF UNREGISTERED SECURITIES.

The following lists set forth information regarding all securities sold or granted by the Registrant from November 30, 2017 through November 30, 2020 that were not registered under the Securities Act, and the consideration, if any, received by the Registrant for such securities:

(a) Stock Option Grants

From November 30, 2017 and through November 30, 2020, the Registrant has granted to its employees, directors, consultants and other service providers options to purchase an aggregate of 6,987,843 shares of common stock under the 2016 Plan and the 2020 Plan, with exercise prices ranging from \$1.02 to \$52.90 per share. The issuances of the securities described above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act or Rule 701 promulgated under the Securities Act as transactions pursuant to compensatory benefit plans. The shares of common stock issued upon the exercise of options are deemed to be restricted securities for purposes of the Securities Act.

(b) Preferred Stock

In October 2017 and August 2018, the Registrant issued and sold to eight accredited investors an aggregate of 9,499,556 shares of Series A convertible preferred stock at a purchase price of \$3.1423 per share, for aggregate consideration of approximately \$30.0 million. Additionally, in October 2017, eight accredited investors converted their previous 2016 Preferred Stock into an aggregate of 2,236,563 shares of Series A convertible preferred stock. These shares of Series A convertible preferred stock converted into 11,736,119 shares of the Registrant's common stock or non-voting common stock. This transaction was exempt from the registration requirements of the Securities Act in reliance upon Section 4(2) of the Securities Act or Regulation D promulgated under the Securities Act.

In May 2019 and March 2020, the Registrant issued and sold to six accredited investors an aggregate of 15,257,692 shares of Series B convertible preferred stock at a purchase price of \$3.9325 per share, for aggregate consideration of approximately \$60.0 million. These shares of Series B convertible preferred stock converted into 15,257,692 shares of the Registrant's common stock or non-voting common stock. This transaction was exempt from the registration requirements of the Securities Act in reliance upon Section 4(2) of the Securities Act or Regulation D promulgated under the Securities Act.

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In August 2020, the Registrant issued and sold to seven accredited investors an aggregate of 3,443,612 shares of Series C convertible preferred stock at a purchase price of \$14.5197 per share, for aggregate consideration of approximately \$50.0 million. These shares of Series C convertible preferred stock converted into 3,443,612 shares of the Registrant's common stock or non-voting common stock. This transaction was exempt from the registration requirements of the Securities Act in reliance upon Section 4(2) of the Securities Act or Regulation D promulgated under the Securities Act.

None of the foregoing transactions involved any underwriters, underwriting discounts or commissions or any public offering, and the Registrant believes each transaction was exempt from the registration requirements of the Securities Act as stated above. All recipients of the foregoing transactions either received adequate information about the Registrant or had access, through their relationships with the Registrant, to such information. Furthermore, the Registrant affixed appropriate legends to the share certificates and instruments issued in each foregoing transaction setting forth that the securities had not been registered and the applicable restrictions on transfer.

ITEM 16. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES.

(a) Exhibits.

<u>Exhibit Number</u>	<u>Description</u>	<u>Form</u>	<u>File No.</u>	<u>Exhibit No.</u>	<u>Exhibit Filing Date</u>	<u>Filed/Furnished Herewith</u>
3.1	Restated Certificate of Incorporation of Prelude Therapeutics Incorporated	10-Q	001-39527	3.1	11/10/2020	
3.2	Restated Bylaws of Prelude Therapeutics Incorporated	10-Q	001-39527	3.2	11/10/2020	
4.1	Form of Common Stock Certificate.	S-1/A	333-248628	4.1	09/16/2020	
4.2	Amended and Restated Investors' Rights Agreement, dated August 21, 2020, by and among the Registrant and certain of its stockholders.	S-1/A	333-248628	4.2	09/16/2020	
4.3	Form of Registration Rights Agreement, by and among the Registrant and certain of its stockholders.					X
5.1*	Opinion of Fenwick & West LLP.					
10.1	Form of Indemnification Agreement with directors and officers.	S-1	333-248628	10.1	09/04/2020	
10.2^	2016 Stock Incentive Plan, as amended, and forms of award agreements.	S-1	333-248628	10.2	09/04/2020	
10.3^	2020 Equity Incentive Plan and forms of award agreements.	S-1/A	333-248628	10.3	09/21/2020	
10.4^	2020 Employee Stock Purchase Plan and forms of award agreements.	S-1/A	333-248628	10.4	09/21/2020	

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Pursuant To 17 C.F.R. Section 200.83**

<u>Exhibit Number</u>	<u>Description</u>	<u>Form</u>	<u>File No.</u>	<u>Exhibit No.</u>	<u>Exhibit Filing Date</u>	<u>Filed/Furnished Herewith</u>
10.5†	Second Amended and Restated Entrepreneur Client License Agreement, dated November 1, 2020, by and between the Registrant and Delaware Innovation Space, Inc.	8-K	001-39527	10.1	11/04/2020	
10.6^*	Executive Employment Agreement, dated December , 2020, by and between the Registrant and Krishna Vaddi.					
10.7^*	Executive Employment Agreement, dated December 8, 2020, by and between the Registrant and Andrew P. Combs.					
10.8^*	Executive Employment Agreement, dated December , 2020, by and between the Registrant and David Mauro.					
21.1	Subsidiaries of the Registrant	S-1	333-248628	21.1	09/04/2020	
23.1*	Consent of Ernst & Young LLP, an independent registered public accounting firm.					
23.2*	Consent of Fenwick & West LLP (included in Exhibit 5.1).					
24.1*	Power of Attorney (included in the signature page to this Registration Statement on Form S-1)					
101.INS	XBRL Instance Document					
101.SCH	XBRL Taxonomy Extension Schema Document.					
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.					
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.					
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.					
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.					

* To be filed by amendment.

† Schedules and exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant agrees to furnish supplementally a copy of any omitted schedule or exhibit to the SEC upon request.

^ Indicates management contract or compensatory plan.

(b) Financial Statement Schedules.

No financial statement schedules are provided because the information called for is not required or is shown either in the financial statements or notes.

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ITEM 17. UNDERTAKINGS.

Inssofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant has duly caused this registration statement on Form S-1 to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Wilmington, State of Delaware, on the _____ day of _____, _____.

PRELUDE THERAPEUTICS INCORPORATED

By: _____
Krishna Vaddi, Ph.D.
Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Krishna Vaddi and Brian Piper, and each of them, as his or her true and lawful attorneys-in-fact, proxies and agents, each with full power of substitution and resubstitution and full power to act without the other, for him or her in any and all capacities, to sign any and all amendments to this registration statement (including post-effective amendments or any abbreviated registration statement and any amendments thereto filed pursuant to Rule 462(b) increasing the number of securities for which registration is sought), and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact, proxies and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact, proxies and agents, or their or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement on Form S-1 has been signed by the following persons in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
_____ Krishna Vaddi, Ph.D.	Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	
_____ Brian Piper, M.B.A.	Chief Financial Officer <i>(Principal Accounting and Financial Officer)</i>	
_____ Paul A. Friedman, M.D.	Chairman and Director	
_____ David Bonita, M.D.	Director	
_____ Mardi C. Dier	Director	

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<u>Signature</u>	<u>Title</u>	<u>Date</u>
_____ Kelvin Neu, M.D.	Director	
_____ Victor Sandor, M.D.C.M.	Director	

REGISTRATION RIGHTS AGREEMENT

This Registration Rights Agreement (this “Agreement”) is made as of [], 2020 by and between Prelude Therapeutics Incorporated, a Delaware corporation (the “Company”), and the persons listed on the attached Schedule A who are signatories to this Agreement (collectively, the “Investors”). Unless otherwise defined herein, capitalized terms used in this Agreement have the respective meanings ascribed to them in Section 1.

RECITALS

WHEREAS, the Company and the Investors wish to provide for certain arrangements with respect to the registration of the Registrable Securities (as defined below) by the Company under the Securities Act (as defined below).

NOW, THEREFORE, in consideration of the mutual promises and covenants set forth herein, and other consideration, the receipt and adequacy of which are hereby acknowledged, the parties hereto agree as follows:

Section 1. Definitions

1.1. Certain Definitions. In addition to the terms defined elsewhere in this Agreement, as used in this Agreement, the following terms have the respective meanings set forth below:

- (a) “Board” shall mean the Board of Directors of the Company.
- (b) “Commission” shall mean the Securities and Exchange Commission or any other federal agency at the time administering the Securities Act.
- (c) “Common Stock” shall mean the voting common stock of the Company, par value \$0.0001 per share.
- (d) “Exchange Act” shall mean the Securities Exchange Act of 1934, as amended, or any similar successor federal statute and the rules and regulations thereunder, all as the same shall be in effect from time to time.
- (e) “Investors’ Rights Agreement” shall mean the Amended and Restated Investors’ Right Agreement, dated as of August 21, 2020, by and among the Company and the investors named therein.
- (f) “Other Investors” shall mean the “Investors”, as defined in those certain Registration Rights Agreement, of even date herewith, entered into by and between the Company and each of [] (collectively, and without taking into account any amendments thereto after the date hereof, the “Other RRAs”).
- (g) “Other Investors’ Registrable Securities” means the Registrable Securities (as defined in each of the Other RRAs) of the Other Investors.

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- (h) “Other Securities” shall mean securities of the Company, other than Registrable Securities or the Other Investors’ Registrable Securities.
- (i) “Person” shall mean any individual, partnership, corporation, company, association, trust, joint venture, limited liability company, unincorporated organization, entity or division, or any government, governmental department or agency or political subdivision thereof.
- (j) “Registrable Securities” shall mean the shares of Common Stock and any Common Stock issued or issuable upon the exercise or conversion of any other securities (whether equity, debt or otherwise) of the Company now owned or hereafter acquired by any of the Investors. Registrable Securities held by any of the Investors shall cease to be Registrable Securities of the Investors upon the earliest to occur of the following events: (i) such Registrable Securities have been sold pursuant to an effective Registration Statement; (ii) such Registrable Securities have been sold by the Investors pursuant to Rule 144 (or other similar rule), (iii) such Registrable Securities may be resold by the Investor holding such Registrable Securities without limitations as to volume or manner of sale pursuant to Rule 144; or (iv) ten (10) years after the date of this Agreement. For purposes of this definition, in order to determine whether an Investor is an “affiliate” (as such term is defined and used in Rule 144, and including for determining whether volume or manner of sale limitations of Rule 144 apply) the parties will assume that all convertible securities (whether equity, debt or otherwise) have been converted into Common Stock without regard to any limitations on conversion applicable thereto.
- (k) The terms “register,” “registered” and “registration” shall refer to a registration effected by preparing and filing a Registration Statement in compliance with the Securities Act, and such Registration Statement becoming effective under the Securities Act.
- (l) “Registration Expenses” shall mean all expenses incurred by the Company in effecting any registration pursuant to this Agreement, including, without limitation, all registration, qualification, and filing fees, printing expenses, escrow fees, fees and disbursements of counsel for the Company, up to \$50,000 of reasonable legal expenses of one special counsel for Investors (if different from the Company’s counsel and if such counsel is reasonably approved by the Company) in connection with the preparation and filing of the Resale Registration Shelf, and up to \$50,000 of reasonable legal expenses of one special counsel for Investors (if different from the Company’s counsel and if such counsel is reasonably approved by the Company) per underwritten public offering, blue sky fees and expenses, and expenses of any regular or special audits incident to or required by any such registration, but shall not include Selling Expenses.
- (m) “Registration Statement” means any registration statement of the Company filed with, or to be filed with, the Commission under the Securities Act, including the related prospectus, amendments and supplements to such registration statement, including pre- and post-effective amendments, and all exhibits and all material incorporated by reference in such registration statement as may be necessary to comply with applicable securities laws other than a registration statement (and related prospectus) filed on Form S-4 or Form S-8 or any successor forms thereto.
- (n) “Rule 144” shall mean Rule 144 as promulgated by the Commission under the Securities Act, as such rule may be amended from time to time, or any similar successor rule that may be promulgated by the Commission.

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(o) “Securities Act” shall mean the Securities Act of 1933, as amended, or any similar successor federal statute and the rules and regulations thereunder, all as the same shall be in effect from time to time.

(p) “Selling Expenses” shall mean all underwriting discounts and selling commissions applicable to the sale of Registrable Securities, the fees and expenses of any legal counsel (except as provided in the definition of “Registration Expenses”) and any other advisors any of the Investors engage and all similar fees and commissions relating to the Investors’ disposition of the Registrable Securities.

**Section 2.
Resale Registration Rights**

2.1. Resale Registration Rights.

(a) Following demand by any Investor, the Company shall file with the Commission a Registration Statement on Form S-3 (except if the Company is not then eligible to register for resale the Registrable Securities on Form S-3, in which case such registration shall be on another appropriate form in accordance with the Securities Act) covering the resale of the Registrable Securities by the Investors (the “Resale Registration Shelf”), and the Company shall file such Resale Registration Shelf as promptly as reasonably practicable following such demand, and in any event within sixty (60) days of such demand. Such Resale Registration Shelf shall include a “final” prospectus, including the information required by Item 507 of Regulation S-K of the Securities Act, as provided by the Investors in accordance with Section 2.7. Notwithstanding the foregoing, before filing the Resale Registration Shelf, the Company shall furnish to the Investors a copy of the Resale Registration Shelf and afford the Investors an opportunity to review and comment on the Resale Registration Shelf. The Company’s obligation pursuant to this Section 2.1(a) is conditioned upon the Investors providing the information contemplated in Section 2.7.

(b) The Company shall use its reasonable best efforts to cause the Resale Registration Shelf and related prospectuses to become effective as promptly as practicable after filing. The Company shall use its reasonable best efforts to cause such Registration Statement to remain effective under the Securities Act until the earlier of the date (i) all Registrable Securities covered by the Resale Registration Shelf have been sold or (ii) all Registrable Securities covered by the Resale Registration Shelf otherwise cease to be Registrable Securities. The Company shall promptly, and within two (2) business days after the Company confirms effectiveness of the Resale Registration Shelf with the Commission, notify the Investors of the effectiveness of the Resale Registration Shelf.

(c) Notwithstanding anything contained herein to the contrary, the Company shall not be obligated to effect, or to take any action to effect, a registration pursuant to Section 2.1(a):

(i) if the Company has and maintains an effective Registration Statement on Form S-3ASR that provides for the resale of an unlimited number of securities by selling stockholders (a “Company Registration Shelf”);

(ii) during the period forty-five (45) days prior to the Company’s good faith estimate of the date of filing of a Company Registration Shelf; or

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(iii) if the Company has caused a Registration Statement to become effective (A) pursuant to this Section 2.1 or (B) Section 2.1 of any of the Other RRAs (and complied with its obligations under Section 2.1(f), below, in connection therewith) during the prior twelve (12) month period.

(d) If the Company has a Company Registration Shelf in place at any time in which the Investors make a demand pursuant to Section 2.1(a), the Company shall file with the Commission, as promptly as practicable, and in any event within fifteen (15) business days after such demand, a “final” prospectus supplement to its Company Registration Shelf covering the resale of the Registrable Securities by the Investors (the “Prospectus”); provided, however, that the Company shall not be obligated to file more than one Prospectus pursuant to this Section 2.1(d) in any six month period to add additional Registrable Securities to the Company Registration Shelf that were acquired by the Investors other than directly from the Company or in an underwritten public offering by the Company. The Prospectus shall include the information required under Item 507 of Regulation S-K of the Securities Act, which information shall be provided by the Investors in accordance with Section 2.7. Notwithstanding the foregoing, before filing the Prospectus, the Company shall furnish to the Investors a copy of the Prospectus and afford the Investors an opportunity to review and comment on the Prospectus.

(e) Deferral and Suspension. At any time after being obligated to file a Resale Registration Shelf or Prospectus, or after any Resale Registration Shelf has become effective or a Prospectus is filed with the Commission (in each case, including pursuant to an Other RRA), the Company may defer the filing of or suspend the use of any such Resale Registration Shelf or Prospectus, upon giving written notice of such action to the Investors with a certificate signed by the Principal Executive Officer of the Company stating that in the good faith judgment of the Board, the filing or use of any such Resale Registration Shelf or Prospectus covering the Registrable Securities would be seriously detrimental to the Company or its stockholders at such time and that the Board concludes, as a result, that it is in the best interests of the Company and its stockholders to defer the filing or suspend the use of such Resale Registration Shelf or Prospectus at such time. The Company shall have the right to defer the filing of or suspend the use of such Resale Registration Shelf or Prospectus for a period of not more than one hundred twenty (120) days from the date the Company notifies the Investors of such deferral or suspension; provided that the Company shall not exercise the right contained in this Section 2.1(e) more than once in any twelve month period. In the case of the suspension of use of any effective Resale Registration Shelf or Prospectus, the Investors, immediately upon receipt of notice thereof from the Company, shall discontinue any offers or sales of Registrable Securities pursuant to such Resale Registration Shelf or Prospectus until advised in writing by the Company that the use of such Resale Registration Shelf or Prospectus may be resumed. In the case of a deferred Prospectus or Resale Registration Shelf filing, the Company shall provide prompt written notice to the Investors of (i) the Company’s decision to file or seek effectiveness of the Prospectus or Resale Registration Shelf, as the case may be, following such deferral and (ii) in the case of a Resale Registration Shelf, the effectiveness of such Resale Registration Shelf. In the case of either a suspension of use of, or deferred filing of, any Resale Registration Shelf or Prospectus, the Company shall not, during the pendency of such suspension or deferral, be required to take any action hereunder (including any action pursuant to Section 2.2 hereof) with respect to the registration or sale of any Registrable Securities pursuant to any such Resale Registration Shelf, Company Registration Shelf or Prospectus.

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(f) Piggy-Back Rights. The Company must provide the Investors with ten (10) days' notice before filing any Resale Registration Shelf or Prospectus pursuant to a request by the Other Investors pursuant to Section 2.1(a) of the Other RRAs, and, upon the Investors' written request, include the Investors as one or more selling stockholders in such Resale Registration Shelf or Prospectus. Section 2.1(g) of the Other RRAs notwithstanding, the securities of the Investors and the Other Investors will be excluded on a *pro rata* basis from such Registration Statement if any such exclusion is deemed necessary in order to comply with any applicable laws or request from the Commission, Nasdaq or any applicable listing agency.

(g) Other Securities. Any Resale Registration Shelf or Prospectus may include Other Investors' Registrable Securities, Other Securities, and may include securities of the Company being sold for the account of the Company; provided (i) such Other Investors' Registrable Securities are treated in a manner consistent with Section 2.1(f) of the Other RRAs) and (ii) such Other Securities are excluded first from such Registration Statement in order to comply with any applicable laws or request from the Commission, Nasdaq or any applicable listing agency. For the avoidance of doubt, no Other Securities may be included in an underwritten offering pursuant to Section 2.2 without the consent of the Investors except as expressly set forth herein.

2.2. Sales and Underwritten Offerings of the Registrable Securities.

(a) Notwithstanding any provision contained herein to the contrary, the Investors, collectively, shall and subject to the limitations set forth in this Section 2.2, be entitled to demand up to two underwritten public offerings to effect the sale or distribution of Registrable Securities during the term of this Agreement; provided that the Investors and the Other Investors shall be entitled to not more than an aggregate of two underwritten public offerings per calendar year pursuant to this Section 2.2 or Section 2.2 of the Other RRAs.

(b) If the Investors intend to effect an underwritten public offering pursuant to a Resale Registration Shelf or Company Registration Shelf to sell or otherwise distribute Registrable Securities, they shall so advise the Company and provide as much notice to the Company as reasonably practicable (and in any event not less than fifteen (15) business days prior to the Investors' request that the Company file a prospectus supplement to a Resale Registration Shelf or Company Registration Shelf).

(c) In connection with any offering initiated by the Investors pursuant to this Section 2.2 involving an underwriting of shares of Registrable Securities, the Investors shall be entitled to select the underwriter or underwriters for such offering, subject to the consent of the Company, such consent not to be unreasonably withheld, conditioned or delayed.

(d) In connection with any offering initiated by the Investors pursuant to this Section 2.2 involving an underwriting of shares of Registrable Securities, the Company shall not be required to include any of the Registrable Securities in such underwriting unless the Investors (i) enter into an underwriting agreement in customary form with the underwriter or underwriters, (ii) accept customary terms in such underwriting agreement with regard to representations and warranties relating to ownership of the Registrable Securities and authority and power to enter into such underwriting agreement and (iii) complete and execute all questionnaires, powers of attorney, custody agreements, indemnities and other documents as may be requested by such

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underwriter or underwriters. Further, the Company shall not be required to include any of the Registrable Securities in such underwriting if (Y) the underwriting agreement proposed by the underwriter or underwriters contains representations, warranties or conditions that are not reasonable in light of the Company's then-current business or (Z) the underwriter, underwriters or the Investors require the Company to participate in any marketing, road show or comparable activity that may be required to complete the orderly sale of shares by the underwriter or underwriters.

(e) Subject to Section 2.2(f) below, the Company must provide the Investors with not less than ten (10) business days' notice before effecting an underwritten public offering of Other Investors' Registrable Securities (including pursuant to Section 2.2 of the Other RRAs) and Other Securities, and, upon the Investor's written request, include the Registrable Securities requested by Investor in such underwritten public offering.

(f) If the total amount of securities to be sold in any underwritten public offering initiated by the Investors pursuant to this Section 2.2, or any underwritten public offering initiated by the Other Investors pursuant to their registration rights, exceeds the amount that the underwriters determine in their sole discretion is compatible with the success of the offering, then the Company shall be required to include in the offering only that number of such securities, including Registrable Securities (subject in each case to the cutback provisions set forth in this Section 2.2(f)), that the underwriters and the Company determine in their sole discretion shall not jeopardize the success of the offering. If the underwritten public offering has been requested pursuant to Section 2.2(a) of this Agreement or the Other RRAs, the number of shares that are entitled to be included in the registration and underwriting shall be allocated in the following manner: (a) first, shares of Company equity securities that the Company desires to include in such registration shall be excluded and (b) second, Registrable Securities requested to be included in such registration by the Investors and the Other Investors shall be excluded, *pro rata*. To facilitate the allocation of shares in accordance with the above provisions, the Company or the underwriters may round down the number of shares allocated to any of the Investors or the Other Investors to the nearest 100 shares.

2.3. Fees and Expenses. All Registration Expenses incurred in connection with registrations pursuant to this Agreement shall be borne by the Company. All Selling Expenses relating to securities registered on behalf of the Investors shall be borne by the Investors.

2.4. Registration Procedures. In the case of each registration of Registrable Securities effected by the Company pursuant to Section 2.1 hereof (including, for the avoidance of doubt, Section 2.1(f)), the Company shall keep the Investors advised as to the initiation of each such registration and as to the status thereof. The Company shall use its reasonable best efforts, within the limits set forth in this Section 2.4, to:

(a) prepare and file with the Commission such amendments and supplements to such Registration Statement and the prospectuses used in connection with such Registration Statement as may be necessary to keep such Registration Statement effective and current and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such Registration Statement;

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- (b) furnish to the Investors such numbers of copies of a prospectus, including preliminary prospectuses, in conformity with the requirements of the Securities Act, and such other documents as the Investors may reasonably request in order to facilitate the disposition of Registrable Securities;
- (c) use its reasonable best efforts to register and qualify the Registrable Securities covered by such Registration Statement under such other securities or blue sky laws of such jurisdictions in the United States as shall be reasonably requested by the Investors, provided that the Company shall not be required in connection therewith or as a condition thereto to qualify to do business or to file a general consent to service of process in any such states or jurisdictions;
- (d) in the event of any underwritten public offering, and subject to Section 2.2(d), enter into and perform its obligations under an underwriting agreement, in usual and customary form, with the managing underwriter of such offering and take such other usual and customary action as the Investors may reasonably request in order to facilitate the disposition of such Registrable Securities;
- (e) notify the Investors at any time when a prospectus relating to a Registration Statement covering any Registrable Securities is required to be delivered under the Securities Act of the happening of any event as a result of which the prospectus included in such Registration Statement, as then in effect, includes an untrue statement of a material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing. The Company shall use its reasonable best efforts to amend or supplement such prospectus in order to cause such prospectus not to include any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing;
- (f) provide a transfer agent and registrar for all Registrable Securities registered pursuant to such Registration Statement and, if required, a CUSIP number for all such Registrable Securities, in each case not later than the effective date of such registration;
- (g) if requested by an Investor, use reasonable best efforts to cause the Company's transfer agent to remove any restrictive legend from any Registrable Securities, within two business days following such request;
- (h) cause to be furnished, at the request of the Investors, on the date that Registrable Securities are delivered to underwriters for sale in connection with an underwritten offering pursuant to this Agreement, (i) an opinion, dated such date, of the counsel representing the Company for the purposes of such registration, in form and substance as is customarily given to underwriters in an underwritten public offering, addressed to the underwriters, and (ii) a letter or letters from the independent certified public accountants of the Company, in form and substance as is customarily given by independent certified public accountants to underwriters in an underwritten public offering, addressed to the underwriters; and

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(i) cause all such Registrable Securities included in a Registration Statement pursuant to this Agreement to be listed on each securities exchange or other securities trading markets on which Common Stock is then listed.

2.5. The Investors Obligations.

(a) Discontinuance of Distribution. The Investors agree that, upon receipt of any notice from the Company of the occurrence of any event of the kind described in Section 2.4(e) hereof, the Investors shall immediately discontinue disposition of Registrable Securities pursuant to any Registration Statement covering such Registrable Securities until the Investors' receipt of the copies of the supplemented or amended prospectus contemplated by Section 2.4(e) hereof or receipt of notice that no supplement or amendment is required and that the Investors' disposition of the Registrable Securities may be resumed. The Company may provide appropriate stop orders to enforce the provisions of this Section 2.5(a).

(b) Compliance with Prospectus Delivery Requirements. The Investors covenant and agree that they shall comply with the prospectus delivery requirements of the Securities Act as applicable to them or an exemption therefrom in connection with sales of Registrable Securities pursuant to any Registration Statement filed by the Company pursuant to this Agreement.

(c) Notification of Sale of Registrable Securities. The Investors covenant and agree that they shall notify the Company following the sale of Registrable Securities to a third party as promptly as reasonably practicable, and in any event within thirty (30) days, following the sale of such Registrable Securities.

2.6. Indemnification.

(a) To the extent permitted by law, the Company shall indemnify the Investors, and, as applicable, their officers, directors, and constituent partners, legal counsel for each Investor and each Person controlling the Investors, with respect to which registration, related qualification, or related compliance of Registrable Securities has been effected pursuant to this Agreement, and each underwriter, if any, and each Person who controls any underwriter within the meaning of the Securities Act against all claims, losses, damages, or liabilities (or actions in respect thereof) to the extent such claims, losses, damages, or liabilities arise out of or are based upon (i) any untrue statement (or alleged untrue statement) of a material fact contained in any prospectus or other document (including any related Registration Statement) incident to any such registration, qualification, or compliance, or (ii) any omission (or alleged omission) to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, or (iii) any violation or alleged violation by the Company of the Securities Act, the Exchange Act, any state securities law, or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities law applicable to the Company and relating to action or inaction required of the Company in connection with any such registration, qualification, or compliance; and the Company shall pay as incurred to the Investors, each such underwriter, and each Person who controls the Investors or underwriter, any legal and any other expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability, or action; provided, however, that the indemnity contained in this Section 2.6(a) shall not apply to amounts paid in settlement of any such claim, loss, damage, liability, or action if

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settlement is effected without the consent of the Company (which consent shall not unreasonably be withheld); and provided, further, that the Company shall not be liable in any such case to the extent that any such claim, loss, damage, liability, or expense arises out of or is based upon any violation by such Investor of the obligations set forth in Section 2.5 hereof or any untrue statement or omission contained in such prospectus or other document based upon written information furnished to the Company by the Investors, such underwriter, or such controlling Person and stated to be for use therein.

(b) To the extent permitted by law, each Investor (severally and not jointly) shall, if Registrable Securities held by such Investor are included for sale in the registration and related qualification and compliance effected pursuant to this Agreement, indemnify the Company, each of its directors, each officer of the Company who signs the applicable Registration Statement, each legal counsel and each underwriter of the Company's securities covered by such a Registration Statement, each Person who controls the Company or such underwriter within the meaning of the Securities Act against all claims, losses, damages, and liabilities (or actions in respect thereof) arising out of or based upon (i) any untrue statement (or alleged untrue statement) of a material fact contained in any such Registration Statement, or related document, or (ii) any omission (or alleged omission) to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, or (iii) any violation or alleged violation by such Investor of Section 2.5 hereof, the Securities Act, the Exchange Act, any state securities law, or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities law applicable to such Investor and relating to action or inaction required of such Investor in connection with any such registration and related qualification and compliance, and shall pay as incurred to such persons, any legal and any other expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability, or action, in each case only to the extent that such untrue statement (or alleged untrue statement) or omission (or alleged omission) is made in (and such violation pertains to) such Registration Statement or related document in reliance upon and in conformity with written information furnished to the Company by such Investor and stated to be specifically for use therein; provided, however, that the indemnity contained in this Section 2.6(b) shall not apply to amounts paid in settlement of any such claim, loss, damage, liability, or action if settlement is effected without the consent of such Investor (which consent shall not unreasonably be withheld); provided, further, that such Investor's liability under this Section 2.6(b) (when combined with any amounts such Investor is liable for under Section 2.6(d)) shall not exceed such Investor's net proceeds from the offering of securities made in connection with such registration.

(c) Promptly after receipt by an indemnified party under this Section 2.6 of notice of the commencement of any action, such indemnified party shall, if a claim in respect thereof is to be made against an indemnifying party under this Section 2.6, notify the indemnifying party in writing of the commencement thereof and generally summarize such action. The indemnifying party shall have the right to participate in and to assume the defense of such claim; provided, however, that the indemnifying party shall be entitled to select counsel for the defense of such claim with the approval of any parties entitled to indemnification, which approval shall not be unreasonably withheld; provided further, however, that if either party reasonably determines that there may be a conflict between the position of the Company and the Investors in conducting the defense of such action, suit, or proceeding by reason of recognized claims for indemnity under

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this Section 2.6, then counsel for such party shall be entitled to conduct the defense to the extent reasonably determined by such counsel to be necessary to protect the interest of such party. The failure to notify an indemnifying party promptly of the commencement of any such action, if prejudicial to the ability of the indemnifying party to defend such action, shall relieve such indemnifying party, to the extent so prejudiced, of any liability to the indemnified party under this Section 2.6, but the omission so to notify the indemnifying party shall not relieve such party of any liability that such party may have to any indemnified party otherwise than under this Section 2.6.

(d) If the indemnification provided for in this Section 2.6 is held by a court of competent jurisdiction to be unavailable to an indemnified party with respect to any loss, liability, claim, damage, or expense referred to therein, then the indemnifying party, in lieu of indemnifying such indemnified party hereunder, shall contribute to the amount paid or payable by such indemnified party as a result of such loss, liability, claim, damage, or expense in such proportion as is appropriate to reflect the relative fault of the indemnifying party on the one hand and of the indemnified party on the other in connection with the statements or omissions that resulted in such loss, liability, claim, damage, or expense as well as any other relevant equitable considerations. The relative fault of the indemnifying party and of the indemnified party shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission to state a material fact relates to information supplied by the indemnifying party or by the indemnified party and the parties' relative intent, knowledge, access to information, and opportunity to correct or prevent such statement or omission. In no event, however, shall (i) any amount due for contribution hereunder be in excess of the amount that would otherwise be due under Section 2.6(a) or Section 2.6(b), as applicable, based on the limitations of such provisions and (ii) a Person guilty of fraudulent misrepresentation (within the meaning of the Securities Act) be entitled to contribution from a Person who was not guilty of such fraudulent misrepresentation.

(e) Notwithstanding the foregoing, to the extent that the provisions on indemnification and contribution contained in the underwriting agreement entered into in connection with an underwritten public offering are in conflict with the foregoing provisions, the provisions in the underwriting agreement shall control; provided, however, that the failure of the underwriting agreement to provide for or address a matter provided for or addressed by the foregoing provisions shall not be a conflict between the underwriting agreement and the foregoing provisions.

(f) The obligations of the Company and the Investors under this Section 2.6 shall survive the completion of any offering of Registrable Securities in a Registration Statement under this Agreement or otherwise.

2.7. Information. The Investors shall furnish to the Company such information regarding the Investors and the distribution proposed by the Investors as the Company may reasonably request and as shall be reasonably required in connection with any registration referred to in this Agreement. The Investors agree to, as promptly as practicable (and in any event prior to any sales made pursuant to a prospectus), furnish to the Company all information required to be disclosed in order to make the information previously furnished to the Company by the Investors not misleading. The Investors agree to keep confidential the receipt of any notice received

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pursuant to Section 2.4(e) and the contents thereof, except as required pursuant to applicable law. Notwithstanding anything to the contrary herein, the Company shall be under no obligation to name the Investors in any Registration Statement if the Investors have not provided the information required by this Section 2.7 with respect to the Investors as a selling securityholder in such Registration Statement or any related prospectus.

2.8. Rule 144 Requirements. With a view to making available to the Investors the benefits of Rule 144 and any other rule or regulation of the Commission that may at any time permit the Investors to sell Registrable Securities to the public without registration, the Company agrees to use its reasonable best efforts to:

- (a) make and keep public information available, as those terms are understood and defined in Rule 144 at all times after the date hereof;
- (b) file with the Commission in a timely manner all reports and other documents required of the Company under the Securities Act and the Exchange Act;
- (c) prior to the filing of the Registration Statement or any amendment thereto (whether pre-effective or post-effective), and prior to the filing of any prospectus or prospectus supplement related thereto, to provide the Investors with copies of all of the pages thereof (if any) that reference the Investors; and
- (d) furnish to any Investor, so long as the Investor owns any Registrable Securities, forthwith upon request (i) a written statement by the Company that it has complied with the reporting requirements of Rule 144, (ii) a copy of the most recent annual or quarterly report of the Company and such other reports and documents so filed by the Company, and (iii) such other information as may be reasonably requested by an Investor in availing itself of any rule or regulation of the Commission which permits an Investor to sell any such securities without registration.

2.9. Limitations on Subsequent Registration Rights. From and after the date of this Agreement, the Company shall not, without prior written consent of the Investors, (a) enter into any agreement with any holder or prospective holder of any securities of the Company that would provide to such holder rights with respect to the registration of such securities under the Securities Act or the Exchange Act that would conflict with or adversely affect any of the rights provided to the Investors in this Section 2, or (b) amend the registration rights provisions of the Investors' Rights Agreement or any of the Other RRAs in any manner that would conflict with or adversely affect any of the rights provided to the Investors in this Section 2 (and, in the case of any such amendment, the Company shall notify the Investors in advance of such amendment for it to determine whether such amendment would conflict with or adversely affects their rights in this Section 2); it being understood and agreed that any subsequent agreement of the Company with any holder or prospective holder of any securities of the Company of the same class (or convertible into or exchange for securities of the same class) as the Registrable Securities that grants rights equivalent to the rights of the Investors under this Section 2 will not be prohibited by the terms of this Section 2.9 so long as the inclusion of such holder or prospective holder's securities will not reduce the number of the Registrable Securities of the Holders that are included in any registration hereunder or thereunder.

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proceeding arising out of or relating to this Agreement and the transactions contemplated herein, or for recognition or enforcement of any judgment, and each of the Company and the Investors irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in such New York state court or, to the fullest extent permitted by applicable law, in such federal court. Each of the Company and the Investors hereto agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law.

(c) Each of the Company and the Investors irrevocably and unconditionally waives, to the fullest extent permitted by applicable law, any objection that it may now or hereafter have to the laying of venue of any action or proceeding arising out of or relating to this Agreement and the transactions contemplated herein in any court referred to in Section 3.4(b) hereof. Each of the Company and the Investors hereby irrevocably waives, to the fullest extent permitted by applicable law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court.

(d) EACH OF THE COMPANY AND THE INVESTORS HEREBY IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN ANY LEGAL PROCEEDING DIRECTLY OR INDIRECTLY ARISING OUT OF OR RELATING TO THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY (WHETHER BASED ON CONTRACT, TORT OR ANY OTHER THEORY). EACH OF THE COMPANY AND THE INVESTORS (A) CERTIFIES THAT NO REPRESENTATIVE, AGENT OR ATTORNEY OF ANY OTHER PERSON HAS REPRESENTED, EXPRESSLY OR OTHERWISE, THAT SUCH OTHER PERSON WOULD NOT, IN THE EVENT OF LITIGATION, SEEK TO ENFORCE THE FOREGOING WAIVER AND (B) ACKNOWLEDGES THAT EACH OF THE COMPANY AND THE INVESTORS HAS BEEN INDUCED TO ENTER INTO THIS AGREEMENT BY, AMONG OTHER THINGS, THE MUTUAL WAIVERS AND CERTIFICATIONS IN THIS SECTION.

3.5. Successors, Assigns and Transferees. Any and all rights, duties and obligations hereunder shall not be assigned, transferred, delegated or sublicensed by any party hereto without the prior written consent of the other party; provided, however, that the Investors shall be entitled to transfer Registrable Securities to one or more of their affiliates and, solely in connection therewith, may assign their rights hereunder in respect of such transferred Registrable Securities, in each case, so long as such Investor is not relieved of any liability or obligations hereunder, without the prior consent of the Company. Any transfer or assignment made other than as provided in the first sentence of this Section 3.5 shall be null and void. Subject to the foregoing and except as otherwise provided herein, the provisions of this Agreement shall inure to the benefit of, and be binding upon, the successors, permitted assigns, heirs, executors and administrators of the parties hereto. The Company shall not consummate any recapitalization, merger, consolidation, reorganization or other similar transaction whereby stockholders of the Company receive (either directly, through an exchange, via dividend from the Company or otherwise) equity (the "Other Equity") in any other entity (the "Other Entity") with respect to Registrable Securities hereunder, unless prior to the consummation thereof, the Other Entity assumes, by written instrument, the obligations under this Agreement with respect to such Other Equity as if such Other Equity were Registrable Securities hereunder.

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- 3.6. Entire Agreement. This Agreement, together with any exhibits hereto, constitute the entire agreement between the parties relating to the subject matter hereof and all previous agreements or arrangements between the parties, written or oral, relating to the subject matter hereof are superseded. To the extent there is any conflict between the terms of this Agreement and the terms of the Investors' Rights Agreement, the terms of this Agreement shall govern.
- 3.7. Waiver. No failure on the part of either party hereto to exercise any power, right, privilege or remedy under this Agreement, and no delay on the part of either party hereto in exercising any power, right, privilege or remedy under this Agreement, shall operate as a waiver thereof; and no single or partial exercise of any such power, right, privilege or remedy shall preclude any other or further exercise thereof or of any other power, right, privilege or remedy.
- 3.8. Severability. If any part of this Agreement is declared invalid or unenforceable by any court of competent jurisdiction, such declaration shall not affect the remainder of the Agreement and the invalidated provision shall be revised in a manner that shall render such provision valid while preserving the parties' original intent to the maximum extent possible.
- 3.9. Titles and Subtitles. The titles and subtitles used in this Agreement are used for convenience only and are not to be considered in construing or interpreting this Agreement. All references in this Agreement to sections, paragraphs and exhibits shall, unless otherwise provided, refer to sections and paragraphs hereof and exhibits attached hereto. References to any section in an Other RRA shall be deemed to refer to the equivalent section in the event of any amendment thereto.
- 3.10. Counterparts. This Agreement may be executed in any number of counterparts, each of which shall be enforceable against the parties that execute such counterparts (including by facsimile or other electronic means), and all of which together shall constitute one instrument.
- 3.11. Term and Termination. The Investors' rights to demand the registration of the Registrable Securities under this Agreement, as well as the Company's obligations hereunder other than pursuant to Section 2.6 hereof, shall terminate automatically once all Registrable Securities cease to be Registrable Securities pursuant to the terms of this Agreement.

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IN WITNESS WHEREOF, the parties hereto have executed this Registration Rights Agreement effective as of the day, month and year first above written.

**PRELUDE THERAPEUTICS
INCORPORATED**

By: _____
Name: Krishna Vaddi
Title: Chief Executive Officer

[Signature Page to Registration Rights Agreement]

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IN WITNESS WHEREOF, the parties hereto have executed this Registration Rights Agreement effective as of the day, month and year first above written.

[INVESTOR]

By: _____
Name:
Title:

[INVESTOR]

By: _____
Name:
Title:

[Signature Page to Registration Rights Agreement]

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Schedule A

The Investors

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