UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2020

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 FOR THE TRANSITION PERIOD FROM TO**

Commission File Number 001-39527

PRELUDE THERAPEUTICS INCORPORATED

(Exact name of Registrant as specified in its Charter)

Delaware	**81-1384762**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
200 Powder Mill Road	
Wilmington, Delaware	**19803**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (302) 467-1280

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	PRLD	The Nasdaq Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ☐ NO ☒

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES ☐ NO ☒

Indicate by check mark whether the Registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO ☐

Indicate by check mark whether the Registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit such files). YES ☒ NO ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ☒ NO ☐

The number of shares of Registrant's Common Stock outstanding as of March 12, 2021 was 46,585,860

The registrant was not a public company as of the last business day of its most recently completed second fiscal quarter and therefore, cannot calculate the aggregate market value of its voting and non-voting common equity held by non-affiliates as of such date.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2021 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2020 fiscal year pursuant to Regulation 14A and is incorporated by reference into Part III of this Report.

Table of Contents

PART I

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. All statements other than statements of historical facts are "forward-looking statements" for purposes of these provisions, including those relating to future events or our future financial performance. In some cases, you can identify forward-looking statements by terminology such as "may," "might," "will," "should," "expect," "plan," "anticipate," "project," "believe," "estimate," "predict," "potential," "intend" or "continue," the negative of terms like these or other comparable terminology, and other words or terms of similar meaning in connection with any discussion of future operating or financial performance. These statements are only predictions. All forward-looking statements included in this Annual Report on Form 10-K are based on information available to us on the date hereof, and we assume no obligation to update any such forward-looking statements. Any or all of our forward-looking statements in this document may turn out to be wrong. Actual events or results may differ materially. Our forward-looking statements can be affected by inaccurate assumptions we might make or by known or unknown risks, uncertainties and other factors. We discuss many of these risks, uncertainties and other factors in this Annual Report on Form 10-K in greater detail under the heading "Item 1A—Risk Factors." We caution investors that our business and financial performance are subject to substantial risks and uncertainties.

Item 1. 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 four investigational new drug applications, or INDs, and successfully advanced three of these programs into clinical development with the fourth expected to begin clinical development in the first half of 2021. 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.

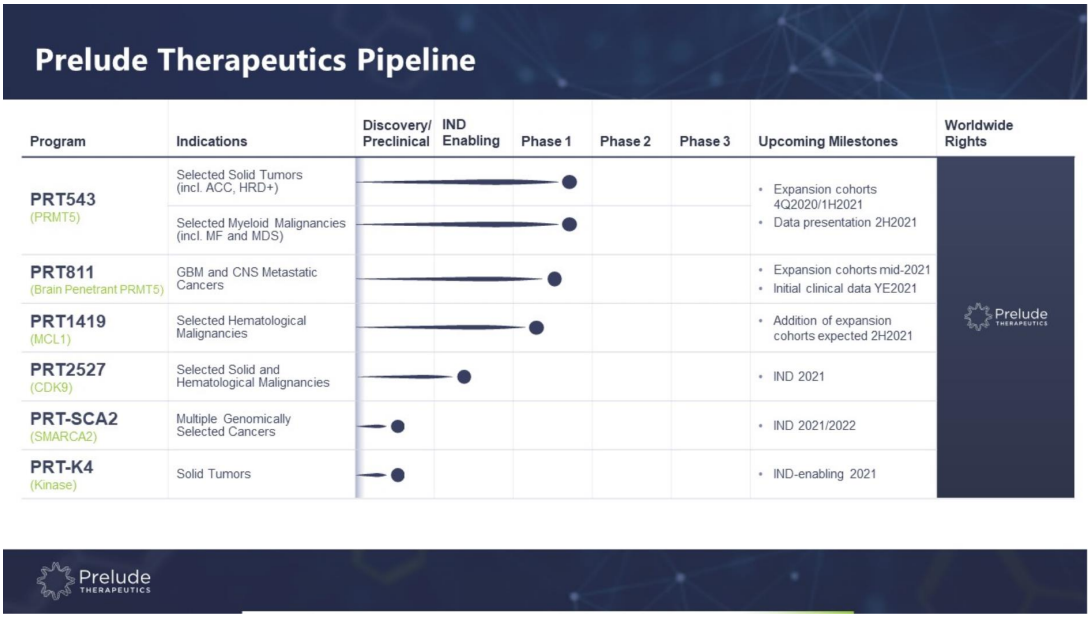
Our lead product candidates are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. The potency and selectivity of our product candidates is supported by preclinical data demonstrating nanomolar inhibition of PRMT5 and no inhibition of related enzymes 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 Annual Report on Form 10-K. We recently completed the dose escalation portion of the trial. The dose expansion portion of the Phase 1 trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the

second quarter of 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 Annual Report on Form 10-K, 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 by mid-2021 and anticipate obtaining initial clinical data from this trial 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 the oral formulation of PRT1419. We expect to add dose expansion and combination cohorts to this Phase 1 clinical trial in the second half of 2021. Additionally, the FDA recently cleared our IND for an intravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of PRT1419, is expected to commence in the first half of 2021 in patients with solid tumors.

Our pipeline is summarized in the figure below:



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.

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 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 have recently completed the dose escalation portion of the ongoing Phase 1 trial for PRT543. The dose expansion portion of the trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the second quarter. 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 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 by mid-2021 and anticipate initial clinical results from this trial 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, the FDA recently cleared our IND for an intravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of PRT1419, is expected to commence in the first half of 2021 in patients with 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, Tabrecta 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:

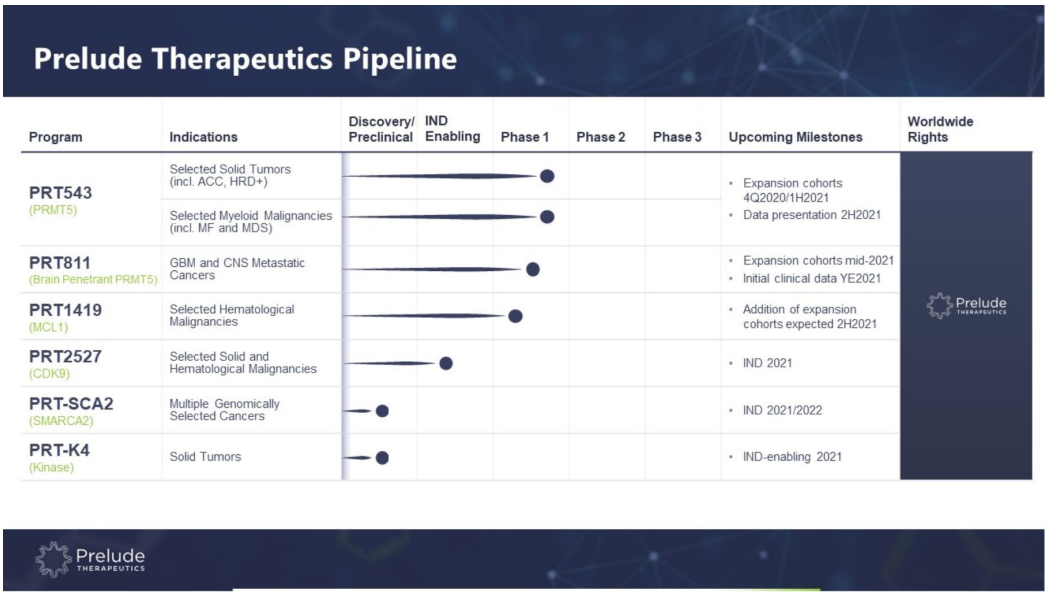
- **Rapidly progress our lead product candidates, PRT543 and PRT811, through clinical development in patients with select solid tumors and hematological malignancies.** Our oral PRMT5 inhibitor candidates target multiple indications, with an initial focus on ACC, HRD+ tumors, myeloid and CNS malignancies, 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 have recently completed the dose escalation portion of the ongoing Phase 1 trial for PRT543. The dose expansion portion of the trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the second quarter. Patient enrollment into the expansion portion of the trial for PRT811 is expected to begin by mid-2021. 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.

- **Expeditiously 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 are enrolling patients into the dose escalation portion of a Phase 1 clinical trial investigating oral PRT1419 in high risk MDS, AML, NHL and MM patients. We expect to add dose expansion and combination cohorts to this Phase 1 clinical trial for the oral formulation of PRT1419 in the second half of 2021. Additionally, the FDA recently cleared our IND for an intravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of PRT1419, is expected to commence in the first half of 2021 in patients with solid tumors.
- **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 four INDs and successfully advanced three of these programs into clinical development, with the fourth program expected to initiate clinical development in the first half of 2021. 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 four INDs and advanced three of these programs into clinical development, with the fourth program expected to initiate clinical development in the first half of 2021. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development 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.



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.

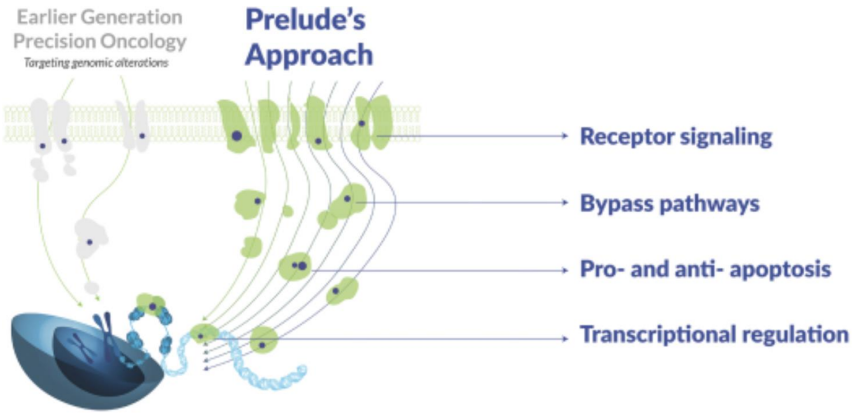
A second-generation of targeted cancer therapies has evolved from the nexus of rapid advances in the understanding of tumor biology and increasingly sophisticated diagnostic platforms that enable identification of subsets of tumors based on

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.



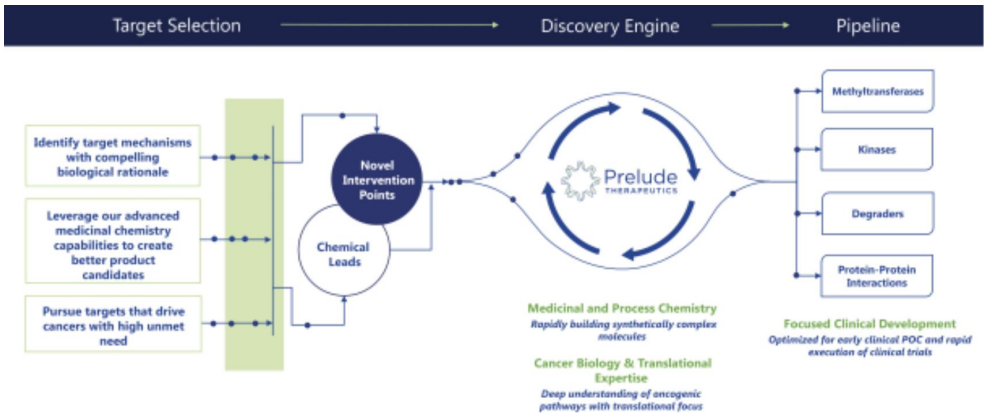
We believe highly selective and potent molecules that target specific oncogenic mechanisms, regardless of target class, can be an effective strategy to address cancers not amenable to earlier and current treatment modalities. These next-generation precision therapies should possess pharmacological, pharmacokinetic, 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.

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.

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, a fourth program expected to enter clinical development in the first half of 2021, 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.

Tumor type	Sample Size of Patients	Median Survival (High PRMT5)	Median Survival (Low PRMT5)	Log rank p-value
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.

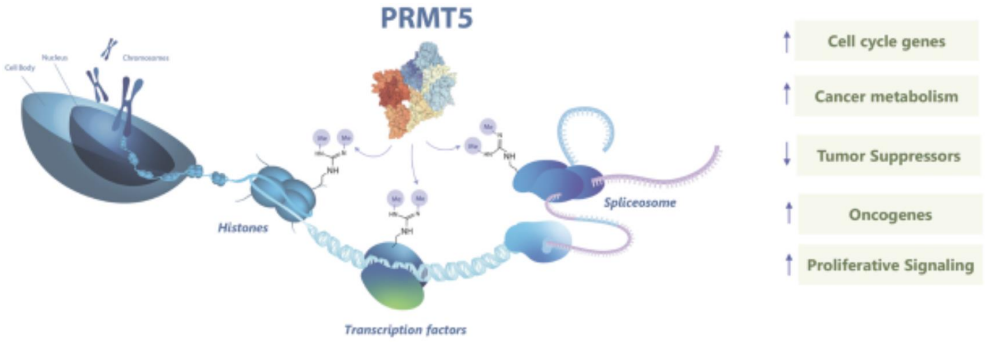
* Where median survival was not explicitly provided in the text, we estimated values from the graphs provided in the publications.

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.

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 *MYBL*1 with the Nuclear Factor 1B, or *NFIB*, 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.

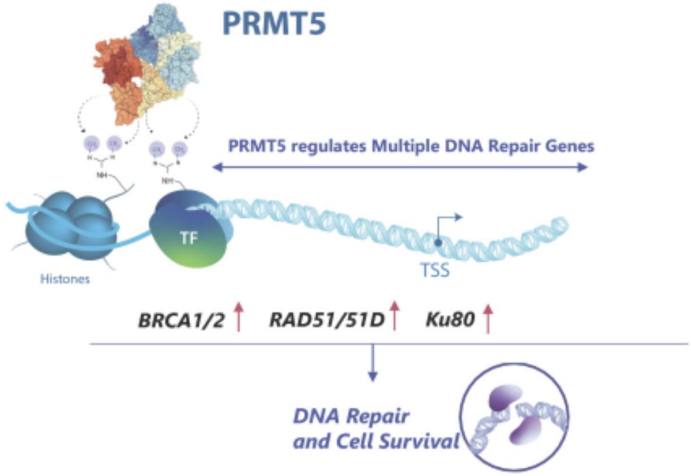
The role of PRMT5 in regulating mRNA splicing may be most relevant in cancers with spliceosomal mutations or those that are dependent on high splicing fidelity, such as GBM. Spliceosomal mutations also occur in more than 50% of MDS patients and at lower frequencies in other tumor types including MF, 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.

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



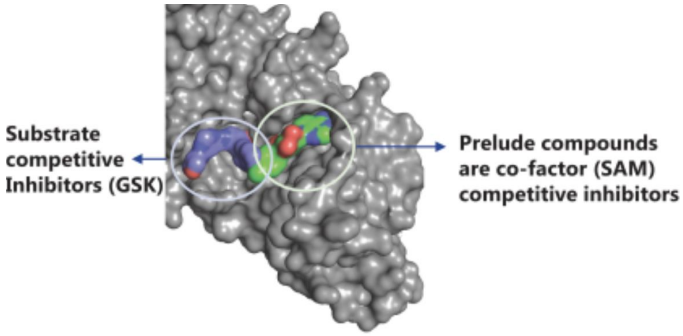
PRMT5 upregulates the expression of DNA repair genes including *BRCA1*, *BRCA2*, *RAD51*, *RAD51D* and *Ku80*. Inhibition of PRMT5 reduces expression of these genes and prevents DNA repair, inducing a state of "*BRCA*ness" and leading to tumor cell death as well as synergy in combination with PARP inhibitors.

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.

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 have recently completed the dose escalation portion of the trial. The dose expansion portion of the Phase 1 trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the second quarter of 2021. 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 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.

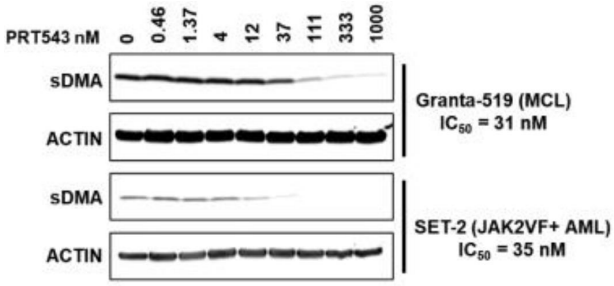
In Vitro Potency and Selectivity

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*



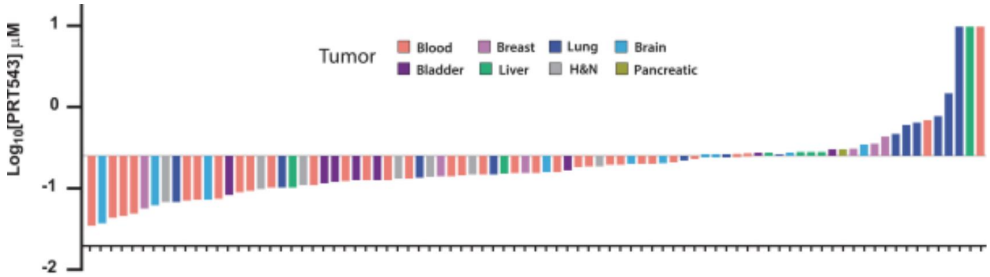
Western blot demonstrating concentration-dependent reduction of symmetrically dimethylated SMD3, a known PRMT5 substrate, following 3 days of PRT543 treatment in indicated cell lines. Granta-519 is a MCL cell line and SET-2 is a JAK2 V617F mutant AML cell line.

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

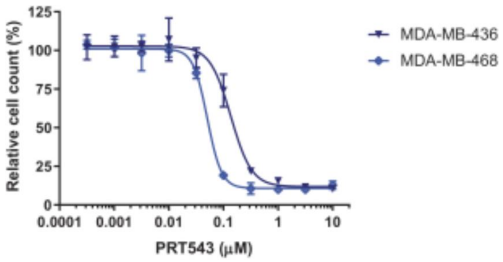
Figure 5: Broad Antiproliferative Activity of PRT543 in a Cancer Cell Line Panel



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.

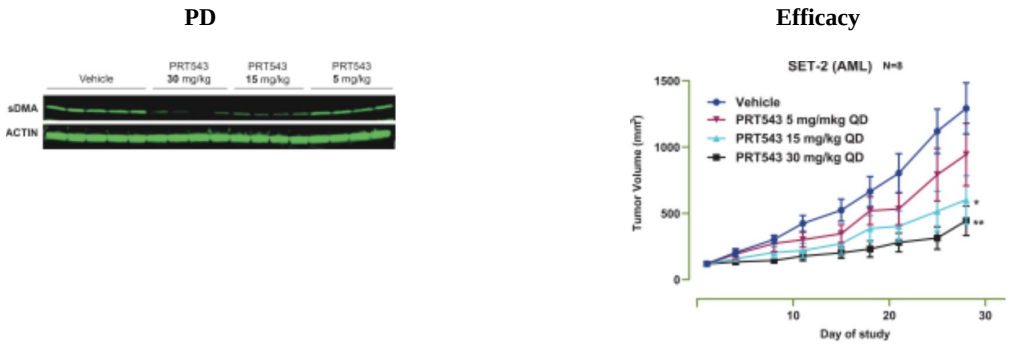


Two HRD+ breast cancer cell lines, MDA-MB-436 and MDA-MB-468, were treated for 10 days with PRT543 and effects on cell proliferation determined. Data are plotted relative to DMSO control.

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 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

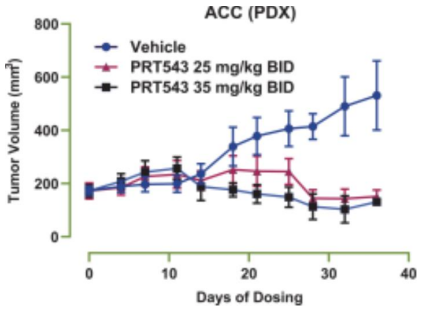


Oral administration of PRT543 leads to dose-dependent decreases in tumor sDMA and TGI in the SET-2 AML model, Western blot showing sDMA reduction in SET-2 tumor tissue collected 4 hours after the last dose, at the end of a 28-day study. Efficacy data represent mean ± SEM with 8 mice/group. * $P < 0.05$,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

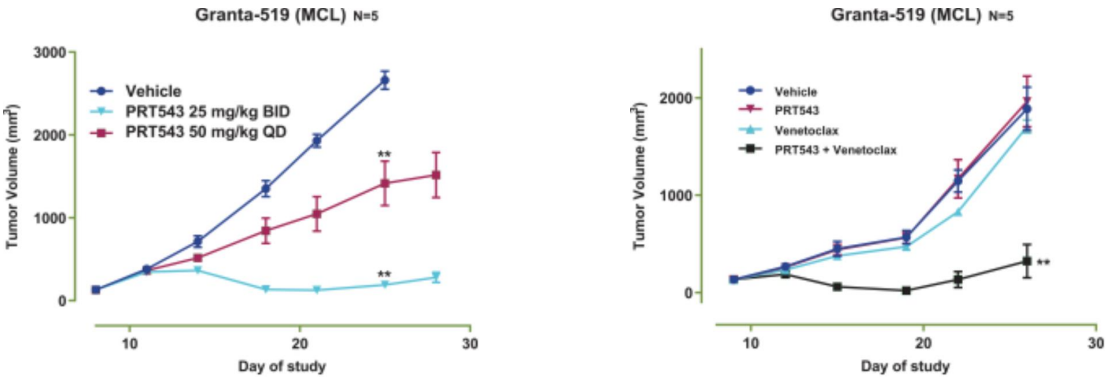
Figure 8. PRT543 Demonstrated Activity in PDX Models of ACC *In Vivo*



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).

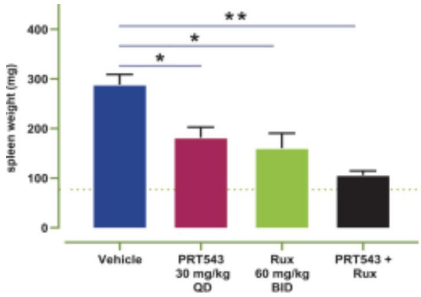
Figure 9. PRT543 is Active as Monotherapy and in Combination *In Vivo*



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* dyrsegulation 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).

Clinical Experience

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

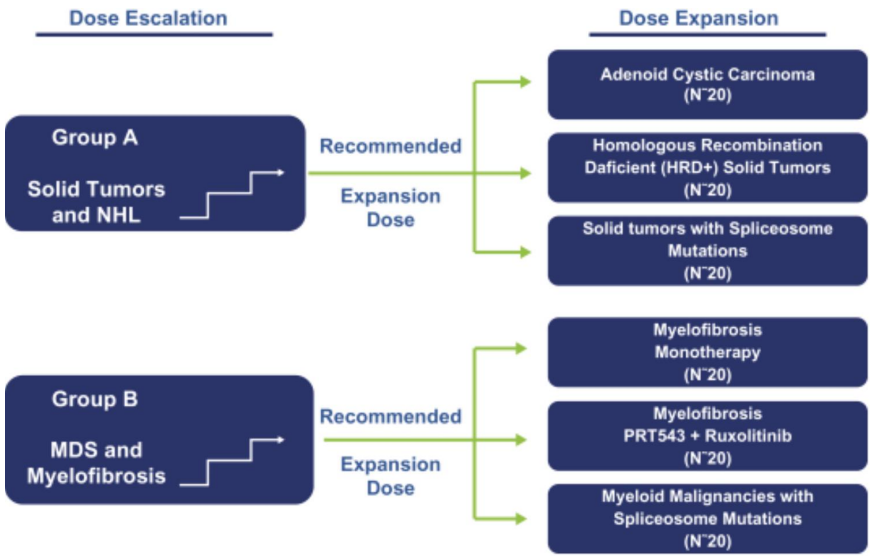
We are currently enrolling a Phase 1, open-label, multicenter, dose expansion clinical trial of monotherapy PRT543 in patients with advanced solid tumors, MF or MDS. We have been encouraged by both the clinical activity and tolerability data that has been observed in 41 patients (29 with advanced solid 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 sequalae 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. We have recently completed the dose escalation portion of the trial. The dose expansion portion of the Phase 1 trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the second quarter of 2021. 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 additional dose expansion cohorts is expected to begin early in the second quarter of 2021. Total expected enrollment is anticipated to be approximately 160 patients. The schema is shown below in Figure 11.

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 Tmax generally occurring between one to three hours with dose-proportional increases in exposure. Half-life 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 µM h versus 96 µM 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) b.i.w	10 mg (n=3) b.i.w	15 mg (n=4) b.i.w	22.5 mg (n=4) b.i.w	45 mg (n=5) b.i.w.	35 mg (n=9)* 5x /q.d.	50 mg (n=4) q.d
Cmax (nM)	52.3	415	525	974	2,574	1,909	2,130
Tmax (h)	4.0	1.7	2.8	1.8	1.0	1.4	1.6
AUC0-t (nM h)	617	4,540	8,060	15,860	35,410	15,120	23,200

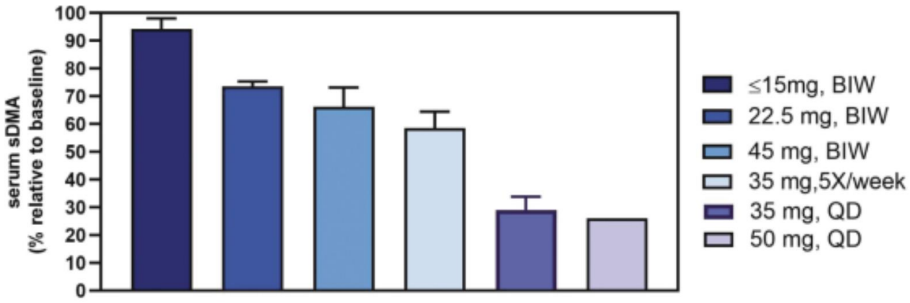
* Day 1 exposure from 35 mg, q.d. and 35mg, 5x dose levels combined. 5x means once a day, for five days, with two days off.

Cmax means the observed maximum plasma concentration after dosing. Tmax means the time to reach the Cmax. AUC0-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

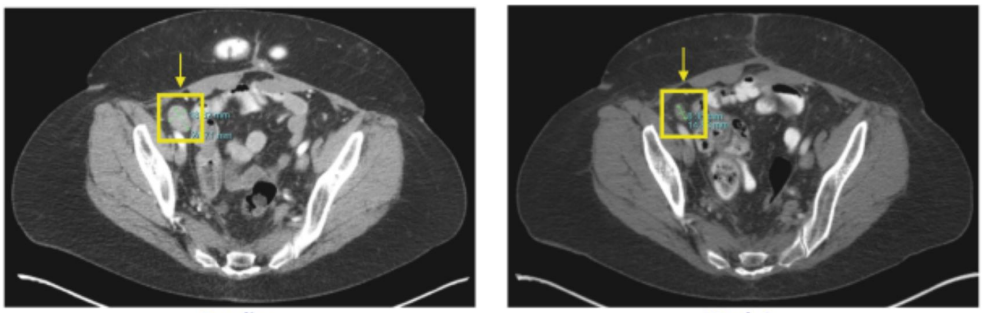


Serum was obtained from patients at various times following administration of PRT543 and analyzed for sDMA levels by LC/MS. The data are shown as % relative to pre-dose levels.

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 ≥ 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.

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
Cmax (nM)	172	486	809	1,343
Tmax (h)	1	1	1.5	1.6
AUC0-t (nM h)	1,120	6,150	15,750	14,888

* 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 45mg 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 expected to begin early in the second quarter of 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 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.

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 initiate by mid-2021 and anticipate initial clinical results from this trial by the end of 2021.

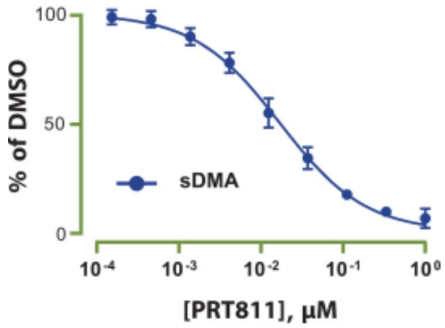
Preclinical

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.

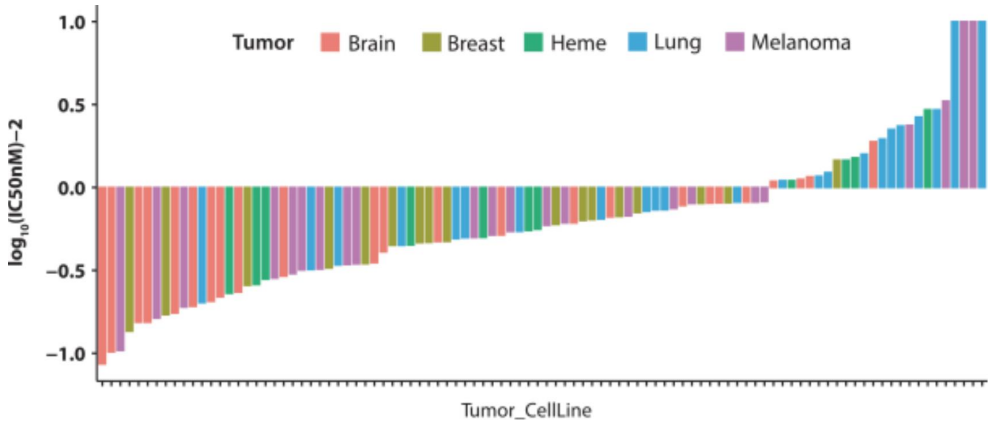
Figure 14. PRT811 is Highly Selective and Demonstrated Potent Inhibition of sDMA in Cells



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).

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

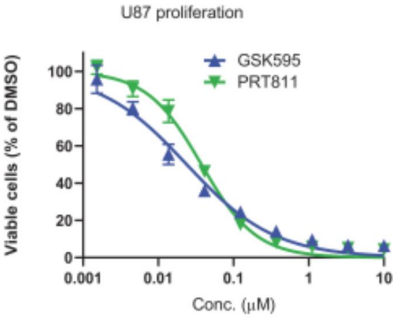


Waterfall plot showing anti-proliferative activity of PRT811 against a panel of 87 cell lines. Cell panel consists of brain cancer cell lines, as well as breast, lung, and melanoma cells lines, the predominant cancer types that metastasize to the brain.

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).

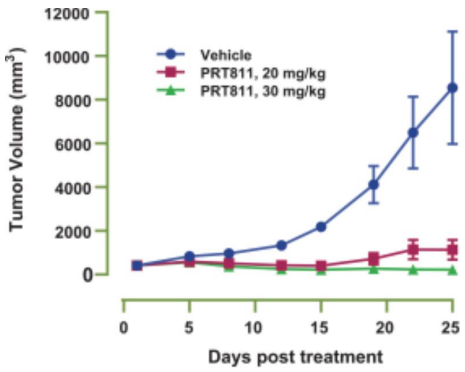
The ability of a compound to effectively achieve high brain exposures has been highlighted most recently by the significantly improved activity of brain penetrant kinase inhibitors compared to their non-brain penetrant counterparts in patients with CNS cancers or with CNS metastasis. In addition, a clear 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.

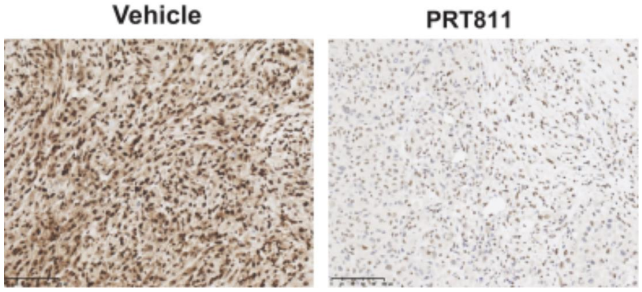
Figure 16. PRT811 Inhibited Tumor Growth in the U-87MG Subcutaneous Xenograft Model



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.

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

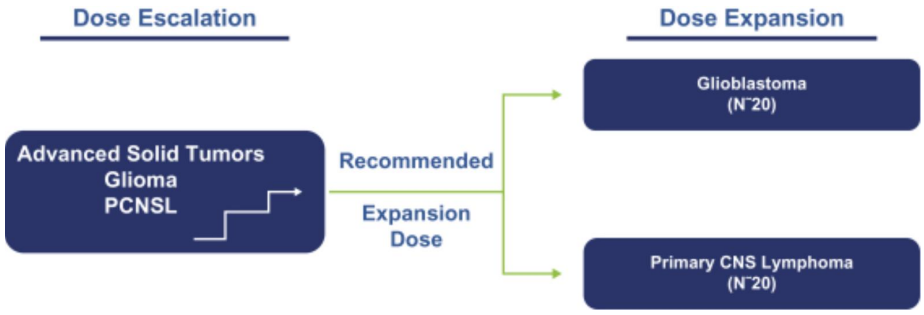
All data are reflective of a data cutoff of September 1, 2020 unless otherwise stated.

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, by mid-2021. The total expected enrollment is approximately 60 patients.

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.

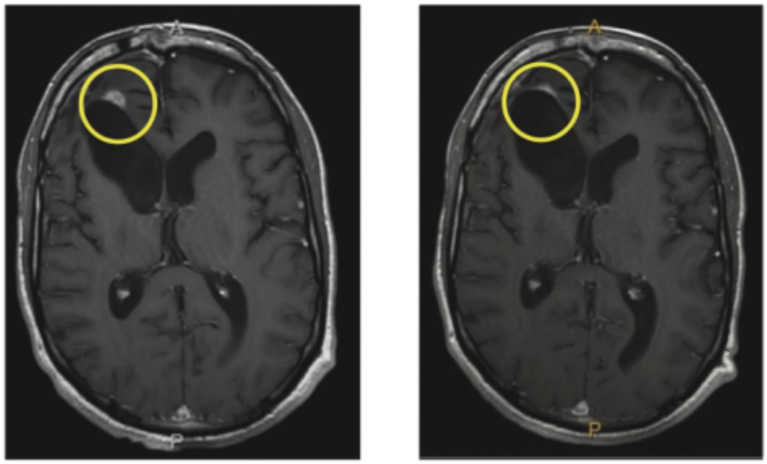
The most commonly reported adverse events, regardless of causality, include constipation (29.4%), nausea (23.5%), vomiting (11.8%) and hyponatremia (11.8%). When examining drug-related adverse events, nausea (17.6%) was most reported. It should be noted that the vast majority, 91.8%, of these adverse 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.

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 Cmax, 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)**
Cmax (nM)	34	58	246	530	751
Tmax (h)	2	2	1.3	1.1	1.0
AUC0-t (nM h)	100	177	498	1,573	1,885

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.

The 300mg q.d. dose cohort is currently ongoing. We expect to initiate the expansion portion of the trial in cancers including GBM, PCNSL, and CNS metastatic solid tumors by mid-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

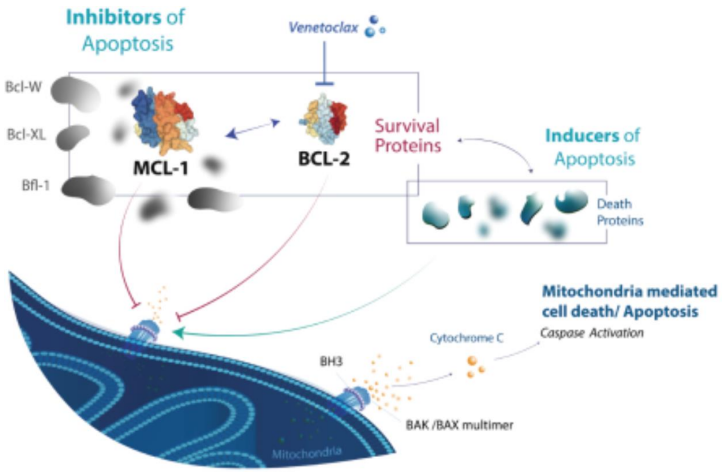
PRT1419 is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. PRT1419 has been optimized to have the PK properties to allow for either oral or IV administration, providing maximal coverage of the target while maintaining an adequate tolerability window. We believe that 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. 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 a Phase 1 clinical trial for the oral formulation of PRT1419. We expect to add dose expansion and combination cohorts to this Phase 1 clinical trial in the second half of 2021. Additionally, the FDA recently cleared our IND for an intravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of PRT1419, is expected to commence in the first half of 2021 in patients with solid tumors.

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 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.

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

Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC_{50} (nM)	150	31	4.5	**80**
Whole Blood IC_{50} (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.

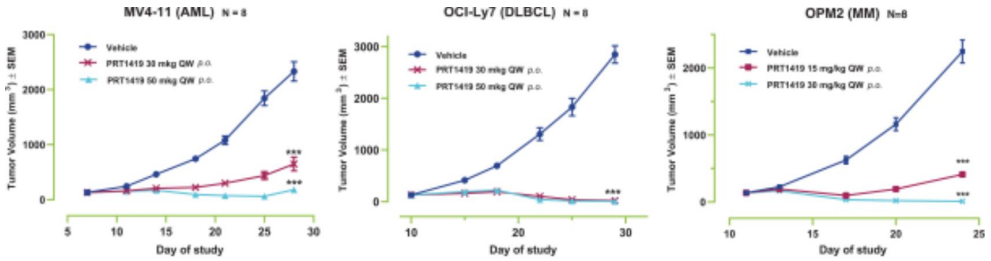
Pharmacokinetics

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).

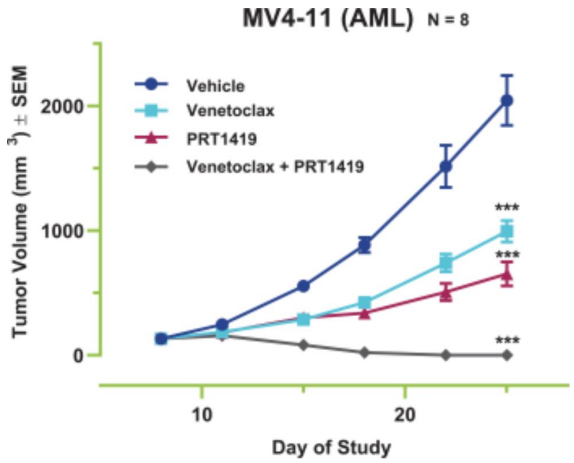
Figure 20. Anti-Tumor Activity in Preclinical Models of Hematologic Malignancies



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



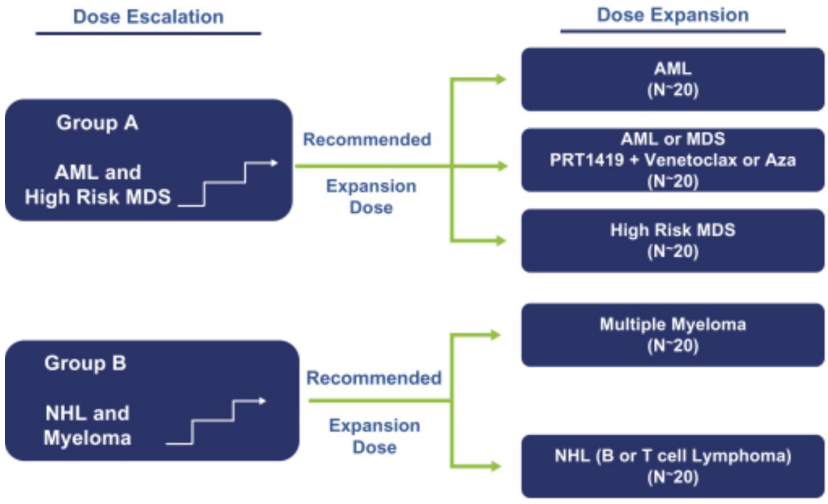
PRT1419 and venetoclax were administered orally as single agents and in combination to tumor-bearing mice (n=8/group). Data represents mean ± SEM (standard error of the means), Venetoclax was dosed at 50 mg/kg; PRT1419 was dosed at 15 mg/kg; *** P value<0.001 vs. Vehicle by Mann-Whitney U test

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 – Oral Formulation

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 a Phase 1 clinical trial for the oral formulation of PRT1419. We expect to add dose expansion and combination cohorts to this Phase 1 clinical trial in the second half of 2021.

Figure 22. PRT1419 Clinical Trial Schema



Clinical Update as of December 16, 2020 – Oral Formulation

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).

PRT1419 – IV Formulation

The FDA recently cleared our IND for an intravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of PRT1419, is expected to commence in the first half of 2021 in patients with solid tumors.

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.

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 of 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.

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 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 Degrader 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 Annual Report on Form 10-K 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 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 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 Degraders

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 degraders. 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 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., Vincerx Pharma, 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.

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.

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 may be sufficient in rare instances, including (1) 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 or (2) when in conjunction with other confirmatory evidence.

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 is 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, based on the agency's threshold determination that it is sufficiently complete to permit substantive review, and FDA 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.

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 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 most 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 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.

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 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.

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 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 offeror or payor knows or should know is likely to influence the beneficiary to order a receive 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. Beginning calendar year 2021, manufacturers must collect information regarding payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants and certified nurse- midwives for reporting in 2022. The reported information is made publicly available on a searchable website.

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.

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.

There have been legislative and judicial efforts to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA, including measures taken during the Trump administration. The Tax Cuts and Jobs Act of 2017, or the Tax Reform 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." In November 2020, the United States Supreme Court held oral arguments on the U.S. Court of Appeals for the Fifth Circuit's decision that held that the individual mandate is unconstitutional. It is uncertain how the United States Supreme court will rule on this case or how healthcare measures of the Biden administration will impact the ACA and our business. 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." In addition, CMS published a final rule that would give states greater flexibility, effective January 1, 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. We cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

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. The Consolidated Appropriations Act, 2021 extended the suspension of the 2% Medicare sequester through March 31, 2021. 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 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 included 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.

In particular, July 24, 2020 and September 13, 2020, the Trump administration 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. The Trump and Biden administrations both issued executive orders intended to favor government procurement from domestic manufacturers. In addition, the Trump administration issued an executive order specifically aimed at the procurement of pharmaceutical products, which instructed the federal government to develop a list of "essential" medicines and then buy those and other medical supplies that are manufactured, including the manufacture of the API, in the United States. It is unclear whether this executive order or something similar will be implemented by the Biden Administration.

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. CMS 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. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule, and it faces uncertain prospects for 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 most 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 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 31, 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 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 that includes 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.

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.

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 Annual Report on Form 10-K are the property of their

respective owners. Solely for convenience, the trademarks and tradenames referred to in this Annual Report on Form 10-K 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.

Available Information

We make available free of charge on our website our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports as soon as reasonably practicable after we electronically file or furnish such materials to the Securities and Exchange Commission, or SEC. The reports are also available at www.sec.gov.

Item 1A. Risk Factors

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 and uncertainties described below, together with the other information contained in this Annual Report on Form 10-K, including our financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations". The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. 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.

Summary of Risk Factors

Our business is subject to a number of risks and uncertainties, including those immediately following this summary. Some of these risks are:

- We are a clinical-stage precision oncology company with a history of operating losses, and we may not achieve or sustain profitability. We anticipate that we will continue to incur losses for the foreseeable future. Our limited operating history may make it difficult for you to evaluate our success to date and to assess our future viability.
- The outbreak of the novel strain of coronavirus, SARS-CoV-2, which causes COVID-19, could adversely impact our business, including our clinical development activities and clinical trials.
- We will need to raise additional funding before we can expect to become profitable from any potential future sales of our products.
- We are very early in our development efforts. Our business is dependent on our ability to advance our current and future product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them.
- Preclinical and clinical development involve a lengthy and expensive process with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our current product candidates or any future product candidates.
- Our product candidates may cause undesirable and unforeseen side effects, which could delay or prevent their advancement into clinical trials or regulatory approval, limit the commercial potential or result in significant negative consequences.
- We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies or technologies that are more advanced or effective than ours.
- We currently rely and expect to continue to rely on third-party manufacturers to produce clinical supply of our product candidates.
- If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under licensed patents is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

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, 2020, we reported a net loss of $56.9 million. As of December 31, 2020, we had an accumulated deficit of $107.4 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. . As of December 31, 2020, our cash and cash equivalents were $218.3 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 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.

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.

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 our existing cash and cash equivalents will enable us to fund our operating expenses, and capital expenditure requirements into 2023. 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;
- 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.

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, 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 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;
- 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.

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 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.

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 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 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 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. See the description of risks under the heading “Risks Related to our Common Stock” 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.

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.

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, 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.

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 the vast majority of 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 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.

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;
- 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 and criminal false claims laws, 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 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.

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, he ACA was enacted, 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 have been legislative and judicial efforts to repeal or replace certain aspects of the ACA, including measures taken during the Trump administration. 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 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. In November 2020, the United States Supreme Court held oral arguments on the U.S. Court of Appeals for the Fifth Circuit's decision that held that the individual mandate is unconstitutional.. 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. The Consolidated Appropriations Act, 2021 extended the suspension of the 2% Medicare sequester through March 31, 2021. 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 Trump 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.

In particular, on July 24, 2020 and September 13, 2020, the Trump administration 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. The Trump and Biden administrations both issued executive orders intended to favor government procurement from domestic manufacturers. In addition, the Trump administration issued an executive order specifically aimed at the procurement of pharmaceutical products, which instructed the federal government to develop a list of "essential" medicines and then buy those and other medical supplies that are manufactured, including the manufacture of the API, in the United States. It is unclear whether this executive order or something similar will be implemented by the Biden Administration.

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 Centers for Medicare and Medicaid Services, or CMS 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 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. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule, and it faces uncertain prospects for 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 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 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 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.

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.

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 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 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.

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 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 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.

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 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 31, 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, 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 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 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 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.

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 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.

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 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 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 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 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.

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 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, 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 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;

- 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

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 purchase price.

An active trading market for our common stock may never be sustained. The market value of our common stock may decrease from the purchase 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 purchase 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;
- 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 initial public offering, or IPO, and has ranged from $23.69 to $95.38 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. The market price for our common stock may be influenced by many factors, including the other risks described in this section of this Annual Report on Form 10-K 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;
- 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.

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 December 31, 2020, our executive officers, directors, beneficial owners of 5% or more of our capital stock and their respective affiliates beneficially owned a substantial portion of our common stock. 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 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.

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 March 12, 2021, 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 75.5% of the voting power, and the former non-voting common stock would represent 24.5% 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 Annual Report on Form 10-K 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 Annual Report on Form 10-K.

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 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 Annual Report on Form 10-K 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 as of the prior June 30 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 as of the prior June 30. 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;
- 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 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.

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 Select 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.

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.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal executive office is located in Wilmington, Delaware where we license a total of approximately 209,500 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.

Item 3. Legal Proceedings.

From time to time, we may be involved in legal proceedings arising in the ordinary course of our business. In addition, we may receive letters alleging infringement of patents or other intellectual property rights. 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, operating results, cash flows or financial conditions should such litigation be resolved unfavorably. 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.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information for Common Stock

Our common stock has been listed on The Nasdaq Global Market under the symbol "PRLD" since September 25, 2020. Prior to that there was no public trading market for our common stock.

Holders of Record

As of March 12, 2021, there were approximately 29 stockholders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

We currently intend to retain future earnings, if any, for use in operation of our business and to fund future growth. We have never declared or paid any cash dividends on our capital stock and do not anticipate paying any cash dividends in the foreseeable future. Payment of cash dividends, if any, in the future will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Unregistered Sales of Equity Securities

From January 1, 2020 through December 31, 2020, we sold and issued the following unregistered securities, which share numbers have been adjusted, as appropriate, to reflect the 1.1566-to-1 reverse stock split which became effective on September 18, 2020:

- Prior to filing our registration statement on Form S-8 in 2020, we granted options to our directors, officers, employees and consultants to purchase an aggregate of 5,026,431 shares of common stock under our 2016 Plan with per share exercise prices ranging from $1.89 to $19.00. 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.

- In May 2019 and March 2020, we 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 our 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 August 2020, we 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 our 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.

Use of Proceeds from Registered Securities

On September 29, 2020, we completed our IPO and sold 9,573,750 shares of common stock at an IPO price of $19.00 per share. The offer and sale of all of the shares in the IPO were registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-248628), which was declared effective by the SEC on September 24, 2020. No additional shares were registered.

We received net proceeds from the IPO of approximately $166.6 million, after deducting underwriting discounts and commissions and offering costs. Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. acted as joint book-running managers of the offering and as representatives of the underwriters. None of the expenses associated with

the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates.

There has been no material change in the planned use of proceeds from our IPO as described in the Prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on September 25, 2020.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Selected Financial Data.

As a Smaller Reporting Company, we have elected not to include Selected Financial Data pursuant to Item 301(c) of Regulation S-K.

Item 7. 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 our financial statements and the related notes and other financial information included elsewhere in this Form 10-K. Some of the information contained in this discussion and analysis contains forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in this Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described below.

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 four investigational new drug applications, or INDs, and successfully advanced three of these programs into clinical development, with the fourth expected to begin clinical development in the first half of 2021. 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 Annual Report on Form 10-K. We have recently completed the dose escalation portion of the trial. The dose expansion portion of the Phase 1 trial is open for the patient cohort with adenoid cystic carcinoma and we now expect to begin patient enrollment into additional solid tumor and myeloid malignancies expansion cohorts early in the second quarter of 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 Annual Report on Form 10-K, 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 by mid-2021 and anticipate obtaining initial clinical data from this trial 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 the oral formulation of PRT1419. We expect to add dose expansion and combination cohorts to this Phase 1 clinical trial in the second half of 2021. Additionally, the FDA recently cleared our IND for an instravenous (IV) formulation of PRT1419. A Phase 1 trial of the IV formulation, which leverages the optimized physicochemical properties of MRT1419, is expected to commence in the first half of 2021 in patients with solid tumors.

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. Our net loss was $56.9 million and $27.6 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of $107.4 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 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 December 31, 2020, we had $218.3 million in cash and cash equivalents. We expect our existing cash and cash equivalents, together with the net proceeds of $161.4 million from the sale of our common stock in January 2021, will enable us to fund our operating expense and capital expenditures into 2023.

COVID-19 Impact

We are continuing to proactively monitor and assess the current coronavirus disease 2019, or COVID-19, global pandemic. Since March 2020 we have been monitoring the potential impact on our business 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, 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 anticipate 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 sale of common stock.

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 Years Ended December 31, 2020 and 2019

The following table sets forth our results of operations for the years ended December 31, 2020 and 2019.

	Year ended December 31,		
(in thousands)	**2020**	**2019**	**Change**
Operating expenses:			
Research and development	$ 48,177	$ 24,279	$ 23,898
General and administrative	10,586	3,830	6,756
Total operating expenses	58,763	28,109	30,654
Loss from operations	(58,763)	(28,109)	(30,654)
Other income, net	1,834	539	1,295
Net loss	$ (56,929)	$ (27,570)	$ (29,359)

Research and Development Expenses

Research and development expenses increased by $23.9 million to $48.2 million for the year ended December 31, 2020 from $24.3 million for the year ended December 31, 2019. The increase was mainly due to increased clinical research 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:

	Year ended December 31,	
(in thousands)	**2020**	**2019**
PRT543	$ 10,641	$ 5,742
PRT811	4,660	3,150
PRT1419	8,258	2,925
Discovery programs	7,981	5,323
Internal costs, including personnel related	16,637	7,139
	$ 48,177	$ 24,279

General and Administrative Expenses

General and administrative expenses increased by $6.8 million to $10.6 million for the year ended December 31, 2020 from $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 and incurred additional costs as we began operating as a public company.

Other Income, net

Other income, net increased by $1.3 million to $1.8 million for the year ended December 31, 2020 from $0.5 million for the year ended December 31, 2019, 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 as well as additional interest earned on the investment of our cash proceeds.

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, we have funded our operations through the sale of convertible preferred stock and common stock. As of December 31, 2020, we had $218.3 million in cash and cash equivalents and had an accumulated deficit of $107.4 million. We expect our existing cash and cash equivalents, together with the net proceeds of $161.4 million from the sale of our common stock in January 2021, will enable us to fund our operating expense and capital expenditures into 2023. 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.

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.

Cash Flows

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

	Years ended December 31,	
(in thousands)	**2020**	**2019**
Cash used in operating activities	$ (46,177)	$ (25,665)
Cash used in investing activities	(621)	(780)
Cash provided by financing activities	246,228	29,729
Net increase in cash and cash equivalents	$ 199,430	$ 3,284

Operating Activities

During the year ended December 31, 2020, we used $46.2 million of cash in operating activities. Cash used in operating activities reflected our net loss of $56.9 million, offset by a $4.6 million net decrease in our operating assets and liabilities and noncash charges of $6.1 million, which consisted of $0.5 million in depreciation and amortization and $5.6 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.

Investing Activities

During the years ended December 31, 2020 and 2019, we used $0.6 million and $0.8 million of cash, respectively, for the purchase of property and equipment.

Financing Activities

During the year ended December 31, 2020, financing activities provided $246.2 million. During the year ended December 31, 2020, we completed our IPO and received net cash of $166.6 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 $0.1 million from the exercise of stock options. During the year ended December 31, 2020, we made $0.3 million in payments for our capital lease obligation.

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.

Off-Balance Sheet Arrangements

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.

Critical Accounting Policies and Estimates

While our significant accounting policies are described in more detail in Note 3 to our audited financial statements included elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies are the most critical to the judgments and estimates used in the preparation of our financial statements.

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.

Share-Based Compensation

We recognize compensation costs related to share-based awards granted to employees and directors, including stock options and vesting restricted stock, based on the estimated fair value of the awards on the date of grant. We estimate the grant date fair value, and the resulting stock-based compensation, using the Black-Scholes option-pricing model. The grant date fair value of the stock-based awards is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards.

We estimate the fair value of stock options using the Black-Scholes option-pricing model, which requires assumptions, including the fair value of our common stock prior to the IPO, volatility, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options, and our expected dividend yield. Certain assumptions used in our Black-Scholes option-pricing model represent management's best estimates and involve a number of variables, uncertainties and assumptions and the application of management's judgment, as they are inherently subjective. If any assumptions change, our stock-based compensation expense could be materially different in the future.

These subjective assumptions are estimated as follows:

Fair value of common stock— Historically, for all periods prior to our IPO, the fair value of the shares of common stock underlying our share-based awards was estimated on each grant date by our board of directors. To determine the fair value of our common stock underlying option grants, our board of directors considered, among other things, valuations of our common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants Practice Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation, or the Practice Aid. Since becoming a public company we have used our stock price to determine fair value of our common stock.

Expected volatility—As a privately held company we did not have any trading history for our common stock; accordingly the expected volatility was estimated based on the average volatility for comparable publicly traded biotechnology companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle or area of specialty. As a public company we have computed the historical volatility of our own stock price and will continue to use the average volatility for comparable publicly traded biotechnology companies until we have ample trading history of our own stock commensurate with the estimated expected term of our options.

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 financial statements included elsewhere in this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our financial statements.

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 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.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are a smaller reporting company as defined by Rule 12b-2 of the Exchange Act and are not required to provide the information required under this item.

Item 8. Financial Statements and Supplementary Data.

INDEX TO FINANCIAL STATEMENTS

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, 2020 and 2019, the related statements of operations, changes in convertible preferred stock and stockholders' equity (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, 2020 and 2019, and the results of its operations and its cash flows for the years then ended in conformity with U.S. generally accepted accounting principles.

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

March 16, 2021

PRELUDE THERAPEUTICS INCORPORATED

BALANCE SHEETS

(in thousands, except share and per share data)	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 218,309	$ 18,879
Prepaid expenses and other current assets	2,500	1,345
Total current assets	220,809	20,224
Property and equipment, net	2,480	1,647
Deferred offering costs	301	—
Total assets	$ 223,590	$ 21,871
Liabilities, convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Capital lease obligation	$ —	$ 258
Accounts payable	3,920	1,974
Accrued expenses and other current liabilities	7,455	2,603
Total current liabilities	11,375	4,835
Other liabilities	32	5
Total liabilities	11,407	4,840
Convertible preferred stock, $0.0001 par value:		
Series A convertible preferred stock: No shares and 13,574,008 shares authorized at December 31, 2020 and 2019, respectively; No shares and 11,736,119 shares issued and outstanding at December 31, 2020 and 2019, respectively	—	36,595
Series B convertible preferred stock: No shares and 18,500,000 shares authorized at December 31, 2020 and 2019, respectively; No shares and 7,628,846 shares issued and outstanding at December 31, 2020 and 2019, respectively	—	29,848
Series C convertible preferred stock: No shares authorized, issued or outstanding at December 31, 2020 and 2019	—	—
Total convertible preferred stock	—	66,443
Commitments (note 7)		
Stockholders' equity:		
Voting common stock, $0.0001 par value: 487,149,741 and 42,000,000 shares authorized at December 31, 2020 and 2019, respectively; 32,595,301 and 3,161,653 shares issued and outstanding at December 31, 2020 and 2019, respectively	3	—
Non-voting common stock, $0.0001 par value: 12,850,259 and no shares authorized at December 31, 2020 and 2019, respectively; 11,110,371 and no shares issued and outstanding at December 31, 2020 and 2019, respectively	1	—
Additional paid-in capital	319,605	1,085
Accumulated deficit	(107,426)	(50,497)
Total stockholders' equity (deficit)	212,183	(49,412)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 223,590	$ 21,871

See accompanying notes to financial statements.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF OPERATIONS

(in thousands, except share and per share data)	Year ended December 31, 2020	2019
Operating expenses:		
Research and development	$ 48,177	$ 24,279
General and administrative	10,586	3,830
Total operating expenses	58,763	28,109
Loss from operations	(58,763)	(28,109)
Other income, net	1,834	539
Net loss	$ (56,929)	$ (27,570)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (4.56)	$ (16.52)
Weighted average common shares outstanding, basic and diluted	12,478,463	1,668,549

See accompanying notes to financial statements.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF CHANGES IN CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)

	Convertible preferred stock						Stockholders' equity (deficit)						
	Series A		Series B		Series C		Voting common stock		Non-voting common stock		Additional paid-in capital	Accumulated deficit	Total
(in thousands, except shares)	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at January 1, 2019	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	11,736,119	36,595	7,628,846	29,848	—	—	3,161,653	—	—	—	1,085	(50,497)	(49,412)
Exercise of stock options	—	—	—	—	—	—	100,545	—	—	—	100	—	100
Sale of Series B convertible preferred stock, net of issuance costs of $58	—	—	7,628,846	29,942			—	—	—	—	—	—	—
Sale of Series C convertible preferred stock, net of issuance costs of $174	—	—	—	—	3,443,612	49,826	—	—	—	—	—	—	—
Conversion of convertible preferred 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 issuance costs of $2,538	—	—	—	—	—	—	9,573,750	1	—	—	166,629	—	166,630
Stock-based compensation expense, including issuance of restricted stock awards	—	—	—	—	—	—	432,301	—	—	—	5,583	—	5,583
Net loss	—	—	—	—	—	—	—	—	—	—	—	(56,929)	(56,929)
Balance at December 31, 2020	—	$ —	—	$ —	—	$ —	32,595,301	$ 3	11,110,371	$ 1	$ 319,605	$ (107,426)	$ 212,183

See accompanying notes to financial statements.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF CASH FLOWS

(in thousands)	Year ended December 31, 2020	2019
Cash flows used in operating activities:		
Net loss	$ (56,929)	$ (27,570)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	542	382
Loss on disposal of property and equipment	11	10
Stock-based compensation	5,583	846
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(1,155)	(1,345)
Accounts payable	1,157	546
Accrued expenses and other liabilities	4,614	1,466
Net cash used in operating activities	(46,177)	(25,665)
Cash flows used in investing activities:		
Purchases of property and equipment	(621)	(780)
Net cash used in investing activities	(621)	(780)
Cash flows provided by financing activities:		
Proceeds from the issuance of common stock upon initial public offering, net of offering costs	166,630	—
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	29,942	29,848
Payment of offering costs associated with January 2021 offering	(12)	—
Payment of capital lease obligation	(258)	(124)
Proceeds from the exercise of stock options	100	5
Net cash provided by financing activities	246,228	29,729
Net increase in cash and cash equivalents	199,430	3,284
Cash and cash equivalents at beginning of year	18,879	15,595
Cash and cash equivalents at end of year	$ 218,309	$ 18,879
Supplemental disclosures:		
Property and equipment in accounts payable	$ 765	$ 66
Offering costs in accrued expenses	$ 265	$ —
Offering costs in accounts payable	$ 24	$ —
Issuance of capital lease obligation in connection with purchase of property and equipment	$ —	$ 382

See accompanying 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.

Since its inception, the Company has incurred operating losses and has an accumulated deficit of $107.4 million at December 31, 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 existing cash and cash equivalents, together with the net proceeds of $161.4 million from the sale of common stock in January 2021 (see Note 11), will be sufficient to fund its operating expenses and capital expenditure requirements into 2023.

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 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

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").

On September 18, 2020, in connection with the Company's initial public offering (IPO) of common stock, 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 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 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 prior to the IPO, 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.

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:

Fixed Asset Type	Estimated useful life
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.

Deferred offering costs

The Company capitalizes costs that are directly associated with in-process equity financings until such financings are consummated, at which time such costs are recorded against the gross proceeds from the applicable financing. If a financing is abandoned, deferred offering costs are expensed. Deferred offering costs were $0.3 million at December 31, 2020.

Comprehensive loss

Comprehensive loss includes net loss and certain changes in stockholders' equity (deficit) that are excluded from net loss. The Company's comprehensive loss was equal to net loss for the years ended December 31, 2020 and 2019.

Stock-Based Compensation

The Company measures share-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards.

Estimating the fair value of share-based awards requires the input of subjective assumptions, including, prior to the IPO, 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 accounts for forfeitures for stock option awards as they occur. The Company uses the Black-Scholes option pricing model to value its stock option awards. The assumptions used in estimating the fair value of share-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, share-based compensation expense could be materially different for future awards.

The expected life of the stock options is estimated using the "simplified method," as the Company has limited 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.

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 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

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,	
	2020	2019
Series A convertible preferred stock	—	11,736,119
Series B convertible preferred stock	—	7,628,846
Unvested restricted stock awards	1,214,767	1,335,349
Stock options	6,839,091	2,269,742
	8,053,858	22,970,056

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 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 ("ASC 842"), which requires a lessee to record a right-of-use asset and a corresponding lease liability on the balance sheet for most leases including operating leases. Lessees will classify leases as either finance or operating leases and lessors classify all leases as sales-type, direct financing or operating leases. The statement of operations presentation and expense recognition for lessees for finance leases is similar to that of capital leases under ASC 840 with separate interest and amortization expense with higher periodic expense in the earlier periods of a lease. For operating leases, the statement of operations presentation and expense recognition is similar to that of operating leases under ASC 840 with single lease cost recognized on a straight-line basis. The standard is effective for the Company beginning January 1, 2022, with early adoption permitted, using a modified retrospective approach. While the Company continues to evaluate the provisions of ASC 842 to determine how it will be impacted, the primary effect of adopting the new standard will be to record a right-of-use asset and a lease liability on the balance sheet for all leases with a term of greater than twelve months regardless of their classification. The adoption of ASC 842 is not expected to have a material impact on the Company's results of operations or cash flows.

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		
(in thousands)	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2020:			
Assets:			
Cash equivalents (Money Market Funds)	$ 217,072	$ —	$ —
December 31, 2019:			
Assets:	$ 18,779	$ —	$ —
Cash equivalents (Money Market Funds)			

5. Property and Equipment

Property and equipment consisted of the following:

	December 31,	
(in thousands)	2020	2019
Lab equipment	$ 3,010	$ 1,842
Leasehold improvements	448	312
Computers	—	10
Furniture and fixtures	105	39
	3,563	2,203
Less accumulated depreciation	(1,083)	(556)
Property and equipment, net	$ 2,480	$ 1,647

Depreciation and amortization expense was $0.5 million and $0.4 million for the years ended December 31, 2020 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, 2020, the Company had $0.1 million of accumulated amortization related to the capital lease. At December 31, 2020, the Company has no further lease payments under the capital lease.

6. Accrued Expenses

Accrued expenses consisted of the following:

(in thousands)	December 31, 2020	December 31, 2019
Compensation and related benefits	$ 3,614	$ 1,631
Research and development	3,421	658
Other	420	314
	$ 7,455	$ 2,603

7. Commitments

Operating Leases

The Company leases office and laboratory space in Wilmington, Delaware under two separate noncancelable leases, which expire in December 2022 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 $1.2 million and $0.9 million during the years ended December 31, 2020 and 2019, respectively, related to these leases.

The future minimum lease payments under the Company's operating lease agreements as of December 31, 2020 are $1.4 million for both 2021 and for 2022, with no commitments thereafter.

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.

401(k) Defined Contribution Plan

The Company sponsors a 401(k) defined-contribution plan covering all employees. Participants are permitted to contribute up to 100% of their eligible annual pretax compensation up to an established federal limit on aggregate participant contributions. The Company provides a safe harbor match with a maximum amount of 4% of the participant's compensation. The Company has not yet made any matching contributions since inception.

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

Preferred Stock Financings

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.

Pursuant to the 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"). The Company determined that the Series B Future Tranche Right did not meet the definition of a freestanding financial instrument as it was not legally detachable. The Series B Future Tranche Right was also evaluated as an embedded derivative and the Company determined it did not meet the definition of a derivative instrument for which

bifurcation would be required. 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 at a price of $14.5197 per share for net proceeds of approximately $49.8 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.

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.

9. 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, 4,485,907 shares were available for future grants as of December 31, 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. As such, on January 1, 2021, 2,185,283 shares were added to the Plan. 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 December 31, 2020. The number of shares of the Company's common stock that may be issued pursuant to rights granted under the ESPP shall automatically increase on January 1st of each year, commencing on January 1, 2021 and continuing for ten years, in an amount equal to one 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. As such, on January 1, 2021, 437,056 shares were added to the ESPP.

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,	
(in thousands)	2020	2019
Research and development	$ 2,585	$ 437
General and administrative	2,998	409
	$ 5,583	$ 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, 2019	588,961	$ 1.11	9.35
Granted	1,703,692	$ 1.84	
Exercised	(19,669)	$ 1.16	
Forfeited	(3,242)	$ 1.02	
Outstanding at December 31, 2019	2,269,742	$ 1.66	9.20
Granted	4,785,630	$ 11.35	
Exercised	(100,545)	$ 0.99	
Forfeited	(115,736)	$ 1.37	
Outstanding at December 31, 2020	6,839,091	$ 8.46	9.17
Exercisable at December 31, 2020	951,669	$ 1.85	8.22

At December 31, 2020, the aggregate intrinsic value of outstanding options and exercisable options was $431.5 million and $66.3 million, respectively.

The following table summarizes information about stock options outstanding and exercisable at December 31, 2020 under the Plan:

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Life (in years)	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$0.31 - $1.66	555,852	7.62	$ 1.23	327,859	$ 1.18
$1.67 - $7.37	2,954,883	8.88	1.89	606,757	1.89
$7.38 - $15.93	3,129,940	9.67	12.85	16,477	12.85
$15.94 - $69.92	198,416	9.90	57.25	576	19.00
	6,839,091			951,669	

The weighted-average grant date fair value of options granted was $10.12 and $1.41 per share for the years ended December 31, 2020 and 2019, respectively. The aggregate intrinsic value of options exercised was $0.4 million and for the year ended December 31, 2020. The Company recorded stock-based compensation expense of $ 4.8 million and $0.4 million for the years ended December 31, 2020 and 2019, respectively, related to stock options. As of December 31, 2020, the total

unrecognized compensation expense related to unvested stock option awards was $45.8 million, which the Company expects to recognize over a weighted-average period of 3.54 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,	
	2020	2019
Expected volatility	115.17%	91.60%
Risk-free interest rate	0.43%	1.87%
Expected life (in years)	6.25	6.25
Expected dividend yield	—	—

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	1,335,349	$ 1.42
Granted	432,301	$ 3.26
Vested	(552,883)	$ 1.37
Unvested balance at December 31, 2020	1,214,767	$ 2.09

The Company recorded stock-based compensation expense of $0.8 million and $0.4 million for the years ended December 31, 2020 and 2019, respectively, related to RSAs. As of December 31, 2020, the total unrecognized expense related to all RSAs was $2.2 million, which the Company expects to recognize over a weighted-average period of 2.71 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, 2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 28,283	$ 13,659
Research and development credits	4,753	2,216
Stock-based compensation	33	—
Gross deferred tax assets	33,069	15,875
Less: valuation allowance	(32,899)	(15,409)
Total deferred tax asset	170	466
Deferred tax liability		
Stock-based compensation	—	(399)
Depreciation	(170)	(67)
Total deferred tax liabilities	(170)	(466)
	$ —	$ —

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, 2020 and 2019. The valuation allowance increased by $17.5 million and $9.2 million during the years ended December 31, 2020 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, 2020	2019
Federal tax benefit at statutory rate	(21.0)%	(21.0)%
State tax, net of federal benefit	(6.5)	(6.9)
Return to provision	—	(0.7)
Permanent differences	1.2	0.4
Research and development	(4.4)	(5.4)
Change in valuation allowance	30.7	33.6
	—%	—%

The following table summarizes carryforwards of federal, state and local net operating losses ("NOL") and research tax credits:

(in thousands)	December 31, 2020	2019
NOL carryforwards - Federal	$ 101,471	$ 49,005
NOL carryforwards - State	101,471	49,005
Research tax credits - Federal	4,720	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, 2020, the Company also had federal and Delaware research and development tax credit carryforwards of $4.7 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, 2020, 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, 2018 and 2019 remain subject to examination by the taxing jurisdictions. The NOL carryforwards remain subject to review until utilized.

11. Subsequent Event

In January 2021, the Company sold 2,875,000 shares of its common stock at a public offering price of $60.00 per share. The Company received net proceeds of $161.4 million after deducting underwriting discounts, commissions, and other offering expenses paid by the Company.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedure

Under the supervision and with the participation of our management, including our Chief Executive Officer (Our principal executive officer) and our Chief Financial Officer (Our principal accounting officer), we evaluated the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act as of December 31, 2020. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on our management's evaluation (with the participation of our Chief Executive Officer and our Chief Financial Officer), as of the end of the period covered by this report, our Chief Executive Officer and our Chief Financial Officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with GAAP. This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of the of the Company's registered public accounting firm due to a transition period established by rules of the SEC for newly public companies. We will be required, under Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting beginning with our Annual Report on Form 10-K for the year ending December 31, 2021. This assessment will need to include disclosure of any material weaknesses identified by our management in our internal control over financial reporting. The SEC defines a material weakness as a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of a company's annual or interim financial statements will not be detected or prevented on a timely basis.

In accordance with the provisions of the Sarbanes-Oxley Act, neither we nor our independent registered public accounting firm has performed an evaluation of our internal control over financial reporting during any period included in this annual report.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2020 that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2021 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2021 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2021 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2021 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 14. Principal Accounting Fees and Services.

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2021 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) *Financial Statements:*

The financial statements required by Item 15(a) are filed as part of this Annual Report on Form 10-K under Item 8 “Financial Statements and Supplementary Data.”

(2) *Financial Statement Schedules*

The financial statement schedules required by Item 15(a) are omitted because they are not applicable, not required or the required information is included in the financial statements or notes thereto as filed in Item 8 of this Annual Report on Form 10-K.

(3) *Exhibits.*

Exhibit Number	Exhibit Title	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
3.1	Restated Certificate of Incorporation of Prelude Therapeutics Incorporated	10-Q	001-39527	3.1	November 10, 2020	
3.2	Restated Bylaws of Prelude Therapeutics Incorporated	10-Q	001-39527	3.2	November 10, 2020	
4.1	Form of Common Stock Certificate	S-1/A	333-248628	4.1	September 16, 2020	
4.2	Amended and Restated Investors’ Rights Agreement, dated August 21, 2020, by and among Prelude Therapeutics Incorporated and certain of its stockholders	S-1/A	333-248628	4.2	September 16, 2020	
4.3	Form of Registration Rights Agreement, by and among Prelude Therapeutics Incorporated and certain of its stockholders	S-1	333-251874	4.3	January 4, 2021	
4.4	Description of Voting Common Stock Registered Under Section 12 of the Securities Exchange Act of 1943, as amended					X
10.1	Form of Indemnification Agreement with directors and officers	S-1	333-248628	10.1	September 4, 2020	
10.2	2016 Stock Incentive Plan, as amended, and forms of award agreements	S-1	333-248628	10.2	September 4, 2020	
10.3	2020 Equity Incentive Plan and forms of award agreements	S-1/A	333-248628	10.3	September 21, 2020	
10.4	2020 Employee Stock Purchase Plan and forms of award agreements	S-1/A	333-248628	10.4	September 21, 2020	
10.5	Second Amended and Restated Entrepreneur Client License Agreement, dated November 1, 2020, by and between Prelude Therapeutics Incorporated and Delaware Innovation Space, Inc.	8-K	001-39527	10.1	November 4, 2020	
10.6	Executive Employment Agreement, dated December 30, 2020, by and between the Prelude Therapeutics Incorporated and Krishna Vaddi	S-1	333-251874	10.6	January 4, 2021	
10.7	Executive Employment Agreement, dated December 19, 2020, by and between the Registrant and Deborah Morosini	S-1	333-251874	10.7	January 4, 2021	

Exhibit Number	Exhibit Title	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.8	Executive Employment Agreement, dated December 19, 2020, by and between the Registrant and Christopher Pierce	S-1	333-251874	10.8	January 4, 2021	
21.1	Subsidiaries of Prelude Therapeutics Incorporated.	S-1	333-248628	21.1	September 4, 2020	
23.1	Consent of Ernst and Young LLP, an independent registered public accounting firms.					X
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					X
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					X
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
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					

* Filed herewith.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

PRELUDE THERAPEUTICS INCORPORATED

Date: March 16, 2021

By: /s/ Krishna Vaddi
Krishna Vaddi, Ph.D
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Krishna Vaddi Krishna Vaddi, Ph.D.	Chief Executive Officer and Director *(Principal Executive Officer)*	March 16, 2021
/s/ Brian Piper Brian Piper, M.B.A.	Chief Financial Officer *(Principal Accounting and Financial Officer)*	March 16, 2021
/s/ Paul A. Friedman Paul A. Friedman, M.D.	Chairman and Director	March 16, 2021
/s/ Julian Baker Julian Baker	Director	March 16, 2021
/s/ David Bonita David Bonita, M.D.	Director	March 16, 2021
/s/ Mardi C. Dier Mardi C. Dier	Director	March 16, 2021
/s/ Victor Sandor Victor Sandor, M.D.C.M.	Director	March 16, 2021

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

As of December 31, 2020, Prelude Therapeutics Incorporated (the "***Company***," "***we***" or "***our***") had one class of securities registered under Section 12 of the Securities Exchange Act of 1934 (the "***Exchange Act***"): our common stock, $0.0001 par value per share. Our non-voting common stock are not registered under Section 12 of the Exchange Act. The following summary describes the material terms of our capital stock. The description of capital stock is qualified by reference to our certificate of incorporation, our bylaws and our investors rights agreement (the "***IRA***"), our registration rights agreement (the "***Post-IPO RRA***") with certain of our stockholders (the "***RRA Investors***") which are included as exhibits to our most recent Annual Report on Form 10-K and to the applicable provisions of the Delaware General Corporation Law.

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.

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 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.

Registration Rights

Certain holders of 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.

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.

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 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.

- *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.

- *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 is not listed for trading on any securities exchange and we do not plan to list the non-voting common stock on any securities exchange.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-249032) pertaining to the 2016 Stock Incentive Plan, 2020 Equity Incentive Plan, and 2020 Employee Stock Purchase Plan of Prelude Therapeutics Incorporated of our report dated March 16, 2021, with respect to the financial statements of Prelude Therapeutics Incorporated included in this Annual Report (Form 10-K) for the year ended December 31, 2020.

/s/ Ernst & Young LLP

Philadelphia, Pennsylvania
March 16, 2021

Exhibit 31.1

CERTIFICATION PURSUANT TO RULE 13a-14(a) OR 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Krishna Vaddi, certify that:

1. I have reviewed this annual report on Form 10-K of Prelude Therapeutics Incorporated;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2021

/s/ Krishna Vaddi

Krishna Vaddi, Ph.D.
Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO RULE 13a-14(a) OR 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Brian Piper, certify that:

1. I have reviewed this annual report on Form 10-K of Prelude Therapeutics Incorporated;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2021

/s/ Brian Piper

Brian Piper, M.B.A.
Chief Financial Officer
(Principal Accounting and Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Krishna Vaddi, Chief Executive Officer of Prelude Therapeutics Incorporated (the "Company"), do hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

1. the Annual Report on Form 10-K of the Company for the fiscal year ended December 31, 2020 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 16, 2021

/s/ Krishna Vaddi
Krishna Vaddi, Ph.D.
Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Brian Piper, Chief Financial Officer of Prelude Therapeutics Incorporated (the "Company"), do hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

1. the Annual Report on Form 10-K of the Company for the fiscal year ended December 31, 2020 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 16, 2021

/s/ Brian Piper
Brian Piper, M.B.A.
Chief Financial Officer
(Principal Accounting and Financial Officer)