

PROSPECTUS SUPPLEMENT
(To Prospectus Dated November 24, 2021)



4,496,744 Shares of Common Stock

Pre-Funded Warrants to Purchase 12,895,256 Shares of Common Stock

We are offering 4,496,744 shares of our common stock and, in lieu of common stock to certain investors that so choose, pre-funded warrants to purchase 12,895,256 shares of common stock in this offering.

Our voting common stock is quoted on the Nasdaq Global Select Market under the symbol "PRLD." On May 17, 2023, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$6.30 per share.

The purchase price of each pre-funded warrant sold in this offering equals the price at which a share of common stock is sold to the public in this offering, minus \$0.0001, and the exercise price of each pre-funded warrant equals \$0.0001 per share. This prospectus supplement also relates to the offering of the shares of common stock issuable upon exercise of such pre-funded warrants.

We have two classes of common stock: the voting common stock and the non-voting common stock. For a description of the rights of the voting common stock and non-voting common stock, please see "Description of Capital Stock" beginning on page 18 of the accompanying prospectus, as supplemented by the documents incorporated by reference herein and therein. Unless otherwise noted, all references in this prospectus supplement to our "common stock" refer to our voting common stock. Our non-voting common stock is not listed for trading on any securities exchange. There is no established public trading market for the pre-funded warrants, and we do not expect a market to develop. We do not intend to list the pre-funded warrants on the Nasdaq Global Select Market or any other national securities exchange or nationally recognized trading system.

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

Investing in our securities involves a high degree of risk. See "[Risk Factors](#)" beginning on page S-8 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

	<u>Per Share of Common Stock</u>	<u>Per Pre- Funded Warrant</u>	<u>Total</u>
Public offering price	\$ 5.7500	\$ 5.7499	\$ 100,002,710
Underwriting discounts and commissions ⁽¹⁾⁽²⁾	\$ 0.345	\$ 0.345	\$ 1,200,240
Proceeds, before expenses, to us ⁽²⁾	\$ 5.4050	\$ 5.4049	\$ 98,802,470

(1) See "Underwriters" for a description of the compensation payable to the underwriter.

(2) See below for details regarding the 2,317,787 shares of common stock and 11,595,256 pre-funded warrants for which the underwriters will not receive any underwriting discounts or commissions.

We have granted the underwriter the right to purchase up to an additional 2,608,800 shares of our common stock from us at the public offering price, less the underwriting discounts and commissions, within 30 days from the date of this prospectus supplement. The underwriter expects to deliver the shares of voting and non-voting common stock and the pre-funded warrants against payment on or about May 22, 2023.

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

Investment entities affiliated with our 5% stockholders affiliated with our directors have expressed an interest in purchasing an aggregate of 2,317,787 shares of common stock and 11,595,256 pre-funded warrants in this offering at the public offering price. The underwriter will not receive any underwriting discounts or commissions on securities purchased by such investment entities.

Morgan Stanley

May 18, 2023

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Prospectus Supplement

Prospectus

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 (Registration No. 333-261019) that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. This document is in two parts. The first part is the prospectus supplement, including the documents incorporated by reference herein, which describes the specific terms of this offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference therein. The second part, the accompanying prospectus, including the documents incorporated by reference therein, provides more general information, some of which may not apply to this offering. Before you invest, you should carefully read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, as well as the additional information described in this prospectus supplement under “Where You Can Find More Information.” This prospectus supplement may add to, update or change information contained in the accompanying prospectus. To the extent that any statement we make in this prospectus supplement is inconsistent with statements made in the accompanying prospectus or any documents incorporated by reference therein, the statements made in this prospectus supplement will be deemed to modify or supersede those made in the accompanying prospectus and such documents incorporated by reference therein. However, if any statement in one of these documents is inconsistent with a statement in another document with a later date that is incorporated by reference herein, the statement in the document having the later date modifies and supersedes the earlier statement.

Neither we nor the underwriter has authorized anyone to provide you with any information or to make any representation, other than those contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, or in any free writing prospectus prepared by us or on our behalf or to which we have referred you. Neither we nor the underwriter take any responsibility for, and we provide no assurance as to the reliability of, any other information that others may give you. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates.

We are offering to sell, and seeking offers to buy, shares of our common stock and pre-funded warrants only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the offering of the securities in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of the securities and the distribution of this prospectus supplement outside the United States. This prospectus supplement does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context indicates otherwise, as used in this prospectus supplement and the accompanying prospectus, the terms “Company,” “Prelude,” “Registrant,” “we,” “us” and “our” refer to Prelude Therapeutics Incorporated, a Delaware corporation. The mark “Prelude Therapeutics,” the Prelude logo and all product names are our common law trademarks. All other service marks, trademarks and trade names appearing in this prospectus supplement are the property of their respective owners. Solely for convenience, the trademarks and tradenames referred to in this prospectus supplement 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. This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain additional trade names, trademarks and service marks of other companies, which are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

PROSPECTUS SUMMARY

This summary highlights information contained in other parts of this prospectus supplement or incorporated by reference in this prospectus supplement from our Annual Report on Form 10-K for the year ended December 31, 2022, and our Quarterly Report on Form 10-Q for the period ended March 31, 2023, and our other filings with the SEC listed below under the heading “Incorporation of Information by Reference.” This summary may not contain all the information that you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein carefully, including “Risk Factors” and the financial data and related notes and other information incorporated by reference herein and therein, before making an investment decision. See the section entitled “Special Note Regarding Forward-Looking Statements.”

Our Company

We are a clinical-stage fully integrated oncology company built on a foundation of drug discovery excellence to deliver novel precision cancer medicines to underserved patients. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our clinical development capabilities, we have built an efficient, fully-integrated drug discovery engine and the development expertise necessary to identify compelling biological targets and create new chemical entities, that we rapidly advance into clinical trials. 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 for multiple investigational new drug applications, or INDs, and successfully advanced several programs into clinical trials. In addition, we have other unique programs in various stages of preclinical development.

By focusing on developing molecules using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of multiple distinct programs spanning methyltransferases, kinases, protein-protein interactions and targeted protein degraders. Our pipeline is designed to serve patients with high unmet medical need, where there are limited or no treatment options. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

The following table summarizes our product candidate pipeline:

PROGRAM	CANCER INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	AREAS OF CLINICAL FOCUS
CDK9 PRT2527	Selected solid and hematologic malignancies	▶			CLL, Lymphoma
MCL1 PRT1419	Selected hematologic malignancies and solid tumors	▶			AML, CLL, Lymphoma
CDK4/6 PRT3645	Selected solid tumors	▶			Breast Cancer, Gliomas, HNSCC, Lung, and Endometrial cancers
SMARCA2 PRT3789 (IV)	Multiple genomically-selected cancers	▶			SMARCA4 mutated NSCLC and Other cancers
SMARCA2 (Oral)	Multiple genomically-selected cancers	▶			SMARCA4 mutated NSCLC and Other cancers
New Programs (Multiple targets)	Selected solid and hematologic malignancies	▶			Solid Tumors Heme Malignancies

We have several drug candidates in clinical development, and we believe we can generate proof-of-concept clinical data in the next 12 to 24 months to guide our future regulatory pathways to approval. Our CDK9 and MCL1 inhibitors are selective and potent, with potentially superior safety profiles. Our next generation CDK4/6 inhibitor is specifically designed to be a brain and tissue penetrant and our SMARCA2 molecule is a unique, first-in-class protein degrader, targeting specific patient populations.

Our CDK9 candidate, PRT2527, is designed to be a potent and selective CDK9 inhibitor. In preclinical studies, PRT2527 was shown to reduce MCL1 and MYC protein levels and was highly active in preclinical models at well-tolerated doses. Our preclinical studies suggest that PRT2527 demonstrates high kinase selectivity and potency, providing opportunity for a wider therapeutic index compared to less selective CDK9 inhibitors, allowing for rapid development in combinations.

Preclinical data demonstrated that treatment with PRT2527 depleted oncogenic drivers with short half-lives, such as MYC and MCL1, and effectively induced apoptosis. PRT2527 treatment demonstrated robust efficacy in both hematological malignancies and solid tumor models with MYC dysregulation. Dose dependent increases in exposure and target engagement were observed as evidenced by MYC and MCL1 depletion to levels associated with tumor regression in preclinical models. A Phase 1 trial is underway evaluating escalating IV doses of PRT2527 as a monotherapy in patients with selected solid tumors. On April 18, 2023 we presented the following findings at the 2023 American Association for Cancer Research annual meeting, or the 2023 AACR Annual Meeting:

- In adults with advanced solid tumors, PRT2527 was generally well-tolerated with manageable neutropenia and absence of significant gastrointestinal events or hepatotoxicity. The short half-life of PRT2527 enables acute CDK9 inhibition over a defined period making it potentially suitable for weekly administration without inducing significant toxicity. The observed dose-dependent downregulation of CDK9 transcriptional targets – MYC and MCL-1 mRNA expression in PBMCs isolated from patients treated with PRT2527 –was consistent with the degree of target engagement required for preclinical efficacy. The 15 mg/m² QW dose of PRT2527 was selected for further evaluation in dose-confirmation cohort.

The overall safety profile observed in this study supports further development of PRT2527 in combination with other targeted therapies, including in hematologic malignancies. We expect to present a recommended phase two dose, or RP2D, in hematological malignancies in the second half of 2023.

Our MCL1 candidate, PRT1419, 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. The IV formulation of PRT1419 has demonstrated a desirable pharmacokinetic, pharmacodynamic and safety profile with potential for differentiation from competitor compounds. We are enrolling patients in a Phase 1 solid tumor dose escalation and confirmation study, including a significant number of patients at the recommended expansion dose of 80 mg/m². On April 18, 2023 we presented the following findings at 2023 AACR Annual Meeting:

- PRT1419 demonstrated acceptable safety and tolerability profile in patients with advanced and metastatic solid tumors, with the most common treatment-related adverse events of nausea, vomiting, and diarrhea. Neutropenia was deemed to be dose related. No cardiac toxicity was observed. Pharmacokinetics/pharmacodynamics and safety data in the 80 mg/m² QW PRT1419 dose cohort support further evaluation of this dose in future studies. Induction of activated-BAX and cleaved caspase-3 was observed at 80mg/m² and 120 mg/m² QW PRT1419, suggesting successful MCL-1 inhibition. No tumor reductions met response criteria. Further investigation of PRT1419 in patients with hematologic malignancy is ongoing. We intend to evaluate PRT1419 in hematology malignancies in combinations, with the goal of establishing safety, clinical activity and a RP2D in hematology malignancies in the second half of 2023.

The clinical pharmacodynamic profile of PRT1419 demonstrates the desired level of target engagement, as measured by caspase activation in peripheral mononuclear cells and reduction of CD14+ monocytes to levels associated with tumor regressions in preclinical models of hematological cancers. Advancement in hematological cancers will include monotherapy expansions in chronic lymphocytic leukemia and non-Hodgkin's lymphoma based on a strong rationale for MCL1 inhibition and the need for novel treatments in second line.

In July 2022, we received IND clearance for PRT3645, a brain and tissue penetrant molecule that potently targets CDK4/6 with a biased selectivity for CDK4. A Phase 1 clinical trial has been initiated for PRT3645 in biomarker enriched patients with select tumor types including sarcomas, mesothelioma, gliomas, head and neck cancers and non-small cell lung cancer, in addition to breast cancer with or without brain metastases. We expect to present initial clinical results from the Phase 1 clinical trial in the second half of 2023, and to present a RP2D in solid tumors in the second half of 2024.

In October 2022, we received IND clearance for PRT3789, a potent and selective SMARCA2 protein degrader. SMARCA2 degradation has the greatest potential in patients with SMARCA4 deficient cancers, including approximately 5-10% of non-small cell lung cancers. A Phase 1 dose escalation study of PRT3789 is ongoing. We expect to present a clinical update on its Phase 1 dose escalation study in the second half of 2023. Prelude's discovery team has also identified orally bioavailable and highly selective SMARCA2 degrader preclinical leads which were presented as a poster at the 2023 AACR Annual Meeting.

In November 2022, we announced that we will discontinue the internal development of our two clinical candidates that are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. Discontinuation of the PRMT5 programs will allow us to focus our efforts on our CDK9, MCL1, CDK4/6 and SMARCA2 programs.

At-the-Market Offering

On March 15, 2023, we entered into an Open Market Sale AgreementSM, or the Sale Agreement, with Jefferies LLC, as sales agent and/or principal, pursuant to which we may offer and sell, from time to time to or through Jefferies LLC, shares of common stock having an aggregate offering price of up to \$75.0 million. To date, no shares of our common stock have been offered or sold pursuant to the Sale Agreement. We may terminate the Sale Agreement in accordance with its terms. Pursuant to the terms of the underwriting agreement, we may not sell shares pursuant to the Sale Agreement until the earlier of (i) the exercise in full by the underwriter of its option to purchase additional shares of voting common stock or (ii) 30 days after the date of the underwriting agreement.

Corporate Information

We were formed under the laws of the State of Delaware in February 2016. Our principal executive offices are located at 200 Powder Mill Road, Wilmington, Delaware, 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 supplement. Investors should not rely on any such information in deciding whether to purchase our securities.

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

We qualify as an “emerging growth company” as defined in Rule 405 of the Securities Act of 1933, as amended, or the Securities Act. An emerging growth company may take advantage of relief from certain reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes- Oxley Act of 2002, as amended;
- reduced disclosure about our executive compensation arrangements in our periodic reports, proxy statements and registration statements, including an exemption from complying with new pay versus performance disclosure requirements; and
- exemptions from the requirements of holding non-binding advisory votes on executive compensation or golden parachute arrangements.

In addition, an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. In other words, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. Any decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable. We have elected to use this extended transition period.

We will cease to be an emerging growth company upon the earliest of (1) the end of the fiscal year following the fifth anniversary of our initial public offering (i.e. December 31, 2025); (2) the last day of the fiscal year during which our annual gross revenues are \$1.235 billion or more; (3) the date on which we have, during the previous three-year period, issued more than \$1.0 billion in non-convertible debt securities; and (4) the end of any fiscal year in which the market value of our common stock held by non-affiliates exceeded \$700.0 million as of the end of the second quarter of that fiscal year. We may choose to take advantage of some or all of these reduced reporting burdens.

In addition, we are also a “smaller reporting company,” as defined in Rule 405 under the Securities Act. We may continue to be a smaller reporting company in any given year if either (i) the market value of our stock held by non-affiliates is less than \$250 million as of June 30 in the most recently completed fiscal year or (ii) our

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annual revenue is less than \$100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than \$700 million as of June 30 in the most recently completed fiscal year. 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.

THE OFFERING

Common stock offered by us	4,496,744 shares
Pre-funded warrants offered by us	We are also offering, in lieu of common stock to certain investors, pre-funded warrants to purchase 12,895,256 shares of common stock. The purchase price of each pre-funded warrant equals the price per share at which the shares of common stock are being sold to the public in this offering, minus \$0.0001, and the exercise price of each pre-funded warrant equals \$0.0001 per share. Each pre-funded warrant will be exercisable at any time after the date of issuance. See “Description of Pre-Funded Warrants.” This prospectus supplement also relates to the offering of the shares of common stock issuable upon exercise of such pre-funded warrants.
Option to purchase additional shares	We have granted the underwriter an option for a period of 30 days to purchase up to 2,608,800 additional shares of our common stock.
Common stock to be outstanding immediately after this offering	52,412,999 shares (or 55,021,799 shares if the underwriter exercises its option to purchase additional shares in full).
Non-voting common stock to be outstanding immediately after this offering	12,850,259 shares
Use of proceeds	We estimate that the net proceeds of this offering, after deducting underwriting discounts and commissions and estimated offering expenses, will be approximately \$98.5 million (or approximately \$112.6 million if the underwriter exercises its option to purchase additional shares in full). We currently intend to use the net proceeds of this offering to advance our current clinical pipeline, including PRT2527, PRT1419, PRT3645 and PRT3789; advance our research and discovery efforts including our efforts for a new SMARCA2 oral molecule; and support organizational growth and for working capital and other general corporate purposes. See the section entitled “Use of Proceeds.”
Voting rights	We have two classes of common stock: the voting common stock and non-voting common stock. For a description of the rights of the voting common stock and non-voting common stock, please see “Description of Capital Stock” beginning on page 18 of the accompanying prospectus, as supplemented by the documents incorporated by reference herein and therein.
Indication of interest	Investment entities affiliated with our 5% stockholders affiliated with our directors have expressed an interest in purchasing an aggregate of 2,317,787 shares of common stock and 11,595,256 pre-funded warrants in this offering at the public offering price. The underwriter will not receive any underwriting discounts or commissions on securities purchased by such investment entities.

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Risk factors	You should read the section entitled “Risk Factors” in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
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Nasdaq Global Select Market symbol	“PRLD”
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Our non-voting common stock is not listed for trading on any securities exchange. There is no established public trading market for the pre-funded warrants, and we do not expect a market to develop. We do not intend to list the pre-funded warrants on the Nasdaq Global Select Market or any other national securities exchange or nationally recognized trading system.

The number of shares of our common stock and non-voting common stock to be outstanding after this offering is based on 47,916,255 shares of common stock and non-voting common stock (of which 11,402,037 shares are non-voting common stock) outstanding as of March 31, 2023 (including 131,468 unvested restricted shares outstanding as of March 31, 2023) and excludes:

- 11,868,020 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2023 under our 2016 Stock Incentive Plan, or the 2016 Plan, and our 2020 Equity Incentive Plan, or the 2020 Plan, with a weighted average exercise price of \$10.82 per share;
- 163,750 shares of common stock issuable upon vesting of restricted stock units outstanding as of March 31, 2023 under our 2016 Plan and our 2020 Plan;
- 113,000 shares of common stock issuable upon the exercise of stock options granted after March 31, 2023 under the 2020 Plan with an exercise price of \$6.38; and
- 6,830,064 shares of common stock reserved for future issuance as of March 31, 2023 under our stock-based compensation plans, consisting of (i) 5,040,915 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 1,789,149 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan, or 2020 ESPP.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise of outstanding options and no vesting or settlement of restricted stock units described above, no exercise of the pre-funded warrants offered hereby, and no exercise of the underwriter’s option to purchase additional shares of common stock.

RISK FACTORS

An investment in shares of our common stock or pre-funded warrants involves a high degree of risk. Prior to making a decision about investing in shares of our common stock or pre-funded warrants, you should carefully consider the risk factors described below together with all of the risks, uncertainties and assumptions discussed in our Annual Report on Form 10-K for the year ended December 31, 2022, as updated by our Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, as well as any amendments thereto reflected in subsequent filings with the SEC, each of which are incorporated by reference in this prospectus supplement, and all of the other information in this prospectus supplement, including our financial statements and related notes incorporated by reference herein. If any of the risks incorporated by reference or set forth below occurs, our business, operations and financial condition could suffer significantly. As a result, you could lose some or all of your investment in our common stock or pre-funded warrants. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business, operations and financial condition, or cause the value of our securities to decline.

Risks Related to this Offering

If you purchase shares of our common stock or pre-funded warrants sold in this offering, you will experience immediate and substantial dilution. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

Since the price per share of our common stock being offered is higher than the net tangible book value per share of our common stock, you will suffer dilution with respect to the net tangible book value of the shares of common stock or pre-funded warrants you purchase in this offering. Based on the public offering price of \$5.7500 per share and \$5.7499 per pre-funded warrant and our net tangible book value as of March 31, 2023, if you purchase shares of common stock or pre-funded warrants in this offering, you will suffer immediate dilution of \$0.54 per share with respect to the net tangible book value of the common stock. For a more detailed discussion of the foregoing, see the section entitled “Dilution” below. To the extent outstanding stock options or pre-funded warrants are exercised, or restricted stock units vest and settle, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future, under our Sale Agreement or otherwise, and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled “Use of Proceeds,” and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering to advance our current clinical pipeline, including PRT2527, PRT1419, PRT3645 and PRT3789; advance our research and discovery efforts including our efforts for a new SMARCA2 oral molecule; and support organizational growth and for working capital and other general corporate purposes. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

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

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly. We had 47,916,255 shares of common stock and non-voting common stock outstanding as of March 31, 2023. We filed a registration statement on Form S-3 (Registration No. 333-261019) that was declared effective by the SEC on November 24, 2021, and which registers the offer and sale from time to time by the selling securityholders of up to 31,574,631 shares of our common stock. To the extent shares are sold into the market pursuant to this registration statement on Form S-3, under Rule 144 of the Securities Act or otherwise, particularly in substantial quantities, the market price of our common stock could decline.

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

We may raise money through additional public or private offerings of our equity securities or equity-linked securities. For example, in March 2023, we entered into the Sale Agreement pursuant to which we may offer and sell, from time to time to or through Jefferies LLC, shares of common stock having an aggregate offering price of up to \$75.0 million. Any sales of our equity or equity-linked securities could have a material adverse effect on the market price of our common stock.

In connection with this offering, we and our directors, executive officers and certain of our affiliated stockholders have entered into lock-up agreements for a period of 90 days following this offering. The lock-up agreements are subject to various exceptions, and we and our directors and executive officers may be released from the lock-up agreements prior to the expiration of the lock-up period at the sole discretion of Morgan Stanley & Co. LLC. See the section entitled “Underwriters.” Upon expiration or earlier release of the lock-up agreements, we and our directors and executive officers may sell shares into the market, which could adversely affect the market price of shares of our common stock.

We also expect that significant additional capital may be needed in the future to continue our planned operations. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

In addition, we have a significant number of stock options outstanding, and may also choose to issue additional common stock, or securities convertible into or exchangeable for common stock, in the future in connection with a financing, an acquisition, a litigation settlement, employee arrangements or otherwise. In the event that the outstanding options are exercised, or that we make additional issuances of common stock or other convertible or exchangeable securities, you could experience additional dilution. Furthermore, we cannot assure you that we will be able to issue shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, and investors purchasing our securities in the future may have rights superior to investors purchasing shares in this offering.

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

The dual class structure of our common stock may limit your ability to influence corporate matters. Holders of our common stock are entitled to one vote per share, while holders of our non-voting common stock are not

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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 to become effective upon the completion of this offering. Consequently, if holders of our non-voting common stock following this offering 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, immediately following this offering, 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.

There is no public market for the pre-funded warrants being offered in this offering.

There is no public trading market for the pre-funded warrants being offered in this offering, and we do not expect a market to develop. In addition, we do not intend to list the pre-funded warrants on the Nasdaq Global Select Market or any other national securities exchange or nationally recognized trading system. Without an active trading market, the liquidity of the pre-funded warrants will be limited.

We will not receive a significant amount or any additional funds upon the exercise of the pre-funded warrants.

Each pre-funded warrant is exercisable for \$0.0001 per share of common stock underlying such warrant, which may be paid by way of a cashless exercise, in which the holder would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the pre-funded warrant. Accordingly, we will not receive a significant amount or any additional funds upon the exercise of the pre-funded warrants.

Holders of the pre-funded warrants will have no rights as stockholders until such holders exercise their pre-funded warrants and acquire our shares of common stock.

Until holders of the pre-funded warrants exercise their pre-funded warrants and acquire our shares of common stock, such holders will have no rights with respect to the shares of common stock underlying such pre-funded warrants. Upon exercise of the pre-funded warrants, the holders will be entitled to exercise the rights of a holder of common stock only as to matters for which the record date occurs after the exercise date.

Significant holders or beneficial holders of our common stock may not be permitted to exercise pre-funded warrants that they hold.

A holder of a pre-funded warrant will not be entitled to exercise any portion of any pre-funded warrant which, upon giving effect to such exercise, would cause the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99% of the number of shares of our common stock that would be outstanding immediately after giving effect to the exercise. However, any holder may increase or decrease such percentage to any other percentage not in excess of 19.99% upon at least 61 days' prior notice from the holder to us. As a result, you may not be able to exercise your pre-funded warrants for shares of our common stock at a time when it would be financially beneficial for you to do so. In such circumstance you could seek to sell your pre-funded warrants to realize value, but you may be unable to do so in the absence of an established trading market for the pre-funded warrants.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and documents incorporated herein by reference contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events.

Such statements include, but are not limited to, statements regarding expectations and intentions, costs and expenses, outcome of contingencies, financial condition, results of operations, liquidity, objectives of management, debt financing, our future results of operations and financial position, business strategies, market size, potential growth opportunities, clinical development activities, efficacy and safety profile of our product candidates, timing and results of our pre-clinical studies and clinical trials, the receipt and timing of potential regulatory designations, our ability to maintain and recognize the benefits of certain designations received by product candidates, the achievement of clinical and commercial milestones, the advancement of our technologies and our proprietary product candidates, the successful achievement of the goals of our collaborations, the advancement of the product candidates that are the subjects of these collaborations, the approvals and commercialization of product candidates and other statements that are not historical facts. You can find many of these statements by looking for words like “believes,” “expects,” “anticipates,” “estimates,” “may,” “might,” “should,” “will,” “could,” “plan,” “intend,” “project,” “seek” or similar expressions in this prospectus supplement, in documents incorporated by reference into this prospectus supplement or any free writing prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in our Annual Report on Form 10-K for the year ended December 31, 2022, as updated by our Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, as well as those discussed in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference into this prospectus supplement, the accompanying prospectus and any prospectus supplement or free writing prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this prospectus supplement or, in the case of the accompanying prospectus or documents referred to or incorporated by reference, the date of those documents.

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

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus supplement or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

USE OF PROCEEDS

We estimate that the net proceeds of this offering, after deducting underwriting discounts and commissions and estimated offering expenses, will be approximately \$98.5 million, or \$112.6 million if the underwriter's option to purchase additional shares is exercised in full. We will receive nominal proceeds, if any, from the exercise of the pre-funded warrants.

We currently intend to use the net proceeds of this offering to advance our current clinical pipeline, including PRT2527, PRT1419, PRT3645 and PRT3789; advance our research and discovery efforts including our efforts for a new SMARCA2 oral molecule; and support organizational growth and for working capital and other general corporate purposes.

As of March 31, 2023, we had cash, cash equivalents and marketable securities of \$172.3 million.

Following this offering, we expect our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2025. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under "Risk Factors" in this prospectus supplement and the documents incorporated by reference herein, as well as the amount of cash used in our operations. As a result, our management will have broad discretion over the uses of the net proceeds, if any, we receive in connection with the securities offered pursuant to this prospectus supplement and investors will be relying on the judgment of our management regarding the application of the proceeds.

Pending these uses, we intend to invest the net proceeds in short-term or long-term, investment-grade, interest-bearing securities.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends on our common stock or non-voting common stock in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

DILUTION

If you invest in our common stock or pre-funded warrants in this offering, your ownership interest will be immediately diluted to the extent of the difference between the public offering price per share of our common stock or pre-funded warrant you will pay in this offering and the adjusted net tangible book value per share of our common stock immediately after this offering.

Our net tangible book value as of March 31, 2023 was approximately \$174.7 million, or \$3.65 per share, based upon 47,916,255 shares of common stock and non-voting common stock outstanding as of March 31, 2023. Net tangible book value per share is determined by dividing our total tangible assets (which excludes deferred offering costs) less total liabilities by the number of shares of our common stock and non-voting common stock outstanding as of March 31, 2023. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock and non-voting common stock immediately after this offering.

After giving effect to the issuance and sale of shares of our common stock and pre-funded warrants at the public offering price of \$5.7500 per share of common stock and \$5.7499 per pre-funded warrant (which equals the public offering price per share of the common stock less the \$0.0001 per share exercise price of each such pre-funded warrant) and after deducting underwriting discounts and commissions and estimated offering expenses and excluding proceeds, if any, from the exercise of the pre-funded warrants issued pursuant to this offering or any resulting accounting associated with the pre-funded warrants, our as adjusted net tangible book value as of March 31, 2023 would have been approximately \$273.2 million, or \$5.21 per share. This represents an immediate increase in net tangible book value of \$1.56 per share to existing stockholders and immediate dilution of \$0.54 per share to investors purchasing our common stock, non-voting common stock and pre-funded warrants in this offering at the public offering price.

The following table illustrates this dilution on a per share basis (assuming no exercise of the pre-funded warrants issued in this offering):

Public offering price per share	\$5.7500
Net tangible book value per share as of March 31, 2023	\$3.65
Increase in net tangible book value per share attributable to investors purchasing our common stock, non-voting common stock and pre-funded warrants in this offering	1.56
As adjusted net tangible book value per share after this offering	5.21
Dilution per share to investors purchasing our common stock, non-voting common stock and pre-funded warrants in this offering	<u>\$ 0.54</u>

If holders of pre-funded warrants exercise the pre-funded warrants offered hereby, the as adjusted net tangible book value per share of our common stock after giving effect to this offering would be \$4.18 per share, and the dilution in net tangible book value per share to investors purchasing common stock in this offering would be \$1.57 per share.

If the underwriter exercises its option to purchase 2,608,800 additional shares in full, the as adjusted net tangible book value per share of our common stock after giving effect to this offering would be \$5.22 per share, and the dilution in net tangible book value per share to investors purchasing common stock in this offering would be \$0.53 per share.

The foregoing table and calculations are based on 47,916,255 shares of common stock and non-voting common stock (of which 11,402,037 shares are non-voting common stock) outstanding as of March 31, 2023 (including 131,468 unvested restricted shares outstanding as of March 31, 2023) and excludes:

- 11,868,020 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2023 under the 2016 Plan and the 2020 Plan, with a weighted average exercise price of \$10.82 per share;

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- 163,750 shares of common stock issuable upon vesting of restricted stock units outstanding as of March 31, 2023 under our 2016 Plan and our 2020 Plan;
- 113,000 shares of common stock issuable upon the exercise of stock options granted after March 31, 2023 under the 2020 Plan with an exercise price of \$6.38; and
- 6,830,064 shares of common stock reserved for future issuance as of March 31, 2023 under our stock-based compensation plans, consisting of (i) 5,040,915 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 1,789,149 shares of common stock reserved for future issuance under the 2020 ESPP.

To the extent that outstanding options or pre-funded warrants have been or may be exercised, or restricted stock units have vested or may vest, or other shares are issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to issue additional common stock, or securities convertible into or exchangeable for common stock, in the future. The issuance of these securities could result in further dilution for investors purchasing our common stock in this offering

DESCRIPTION OF PRE-FUNDED WARRANTS

The following is a brief summary of certain terms and conditions of the pre-funded warrants being offered by this prospectus supplement. The following description is subject in all respects to the provisions contained in the pre-funded warrants.

Form

The pre-funded warrants will be issued as individual warrant agreements to the investors. The form of pre-funded warrant will be filed as an exhibit to our Current Report on Form 8-K that we expect to file with the SEC in connection with this offering.

Term

The pre-funded warrants do not expire.

Exercisability

The pre-funded warrants are exercisable at any time after their original issuance. The pre-funded warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and by payment in full of the exercise price in immediately available funds for the number of shares of common stock purchased upon such exercise. As an alternative to payment in immediately available funds, the holder may elect to exercise the pre-funded warrant through a cashless exercise, in which the holder would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the pre-funded warrant. No fractional shares of common stock will be issued in connection with the exercise of a pre-funded warrant.

Exercise Limitations

Under the pre-funded warrants, we may not effect the exercise of any pre-funded warrant, and a holder will not be entitled to exercise any portion of any pre-funded warrant, which, upon giving effect to such exercise, would cause the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99% of the number of shares of our common stock that would be outstanding immediately after giving effect to the exercise. However, any holder may increase or decrease such percentage to any other percentage not in excess of 19.99% upon at least 61 days' prior notice from the holder to us.

Exercise Price

The exercise price per whole share of our common stock purchasable upon the exercise of the pre-funded warrants is \$0.0001 per share of common stock. The exercise price of the pre-funded warrants and the number of shares of our common stock issuable upon exercise of the pre-funded warrants is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our common stock.

Transferability

Subject to applicable laws, the pre-funded warrants may be assigned by the holder without our consent. The pre-funded warrants will be held in definitive form by the warrant agent. The ownership of the pre-funded warrants and any transfers of the pre-funded warrants will be registered in a warrant register maintained by the warrant agent. We will initially act as warrant agent.

Exchange Listing

We do not plan on applying to list the pre-funded warrants on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

Fundamental Transactions

In the event of a fundamental transaction, as described in the pre-funded warrants and generally including but not limited to any reorganization, recapitalization, spin-off or reclassification of our common stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of the voting power of our capital stock, or any person or group becoming the beneficial owner of 50% of the voting power of our capital stock, upon consummation of such a fundamental transaction, the holders of the pre-funded warrants will be entitled to receive upon exercise of the pre-funded warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the pre-funded warrants immediately prior to such fundamental transaction without regard to any limitations on exercise contained in the pre-funded warrants.

No Rights as a Stockholder

Except by virtue of such holder's ownership of shares of our common stock, the holder of a pre-funded warrant does not have the rights or privileges of a holder of our common stock, including any voting rights, until the holder exercises the pre-funded warrant. In the event of certain distributions, including cash dividends, if any, to all holders of our common stock for no consideration, the holder of a pre-funded warrant shall be entitled to participate in such distributions to the same extent as if a holder of shares of our common stock, in which case such distribution shall be held in abeyance for the benefit of such holder until the earlier of such time as the ownership limitations would not be exceeded or the warrant is exercised.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES FOR INVESTORS IN OUR COMMON STOCK AND PRE-FUNDED WARRANTS

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock and pre-funded warrants acquired in this offering. This discussion does not address all aspects of U.S. federal income taxes, does not discuss the potential application of the alternative minimum tax or Medicare Contribution tax and does not deal with state or local taxes, U.S. federal gift and estate tax laws, except to the limited extent provided below, or any non-U.S. tax consequences that may be relevant to investors in light of their particular circumstances.

Special rules different from those described below may apply to certain investors that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as:

- insurance companies, banks and other financial institutions;
- tax-exempt organizations (including private foundations) and tax-qualified retirement plans;
- foreign governments and international organizations;
- broker-dealers and traders in securities;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- Non-U.S. Holders (as defined below) that own, or are deemed to own, more than 5% of our common stock (directly, indirectly or by attribution) or more than 5% of our pre-funded warrants;
- persons required for U.S. federal income tax purposes to conform the timing of income accruals to their financial statements under Section 451(b) of the Code;
- “controlled foreign corporations,” “passive foreign investment companies” and corporations that accumulate earnings to avoid U.S. federal income tax;
- persons that hold our common stock as part of a “straddle,” “hedge,” “conversion transaction,” “synthetic security” or integrated investment or other risk reduction strategy;
- U.S. Holders (as defined below) whose functional currency for U.S. tax purposes is not the U.S. dollar;
- persons who do not hold our common stock or pre-funded warrants as “capital assets” within the meaning of Section 1221 of the Code (generally, for investment purposes); and
- partnerships and other pass-through entities, and investors in such pass-through entities (regardless of their places of organization or formation).

Such investors are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them.

Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, possibly retroactively, and are subject to differing interpretations which could result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the Internal Revenue Service, or the IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions or will not take a contrary position regarding the tax consequences described herein, or that any such contrary position would not be sustained by a court.

For the purposes of this discussion, a “U.S. Holder” means a beneficial owner of our common stock or pre-funded warrants, other than a partnership or other pass-through entity, that is, for U.S. federal income tax purposes, (a) an individual citizen or resident of the United States, (b) a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes), created or organized in or under the laws of the United States,

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any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation regardless of its source, or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons (within the meaning of Section 7701(a)(30) of the Code) have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person. A “Non-U.S. Holder” is, for U.S. federal income tax purposes, a beneficial owner of common stock or pre-funded warrants that is not a U.S. Holder or a partnership or other pass-through entity for U.S. federal income tax purposes.

If you are an individual non-U.S. citizen, you may, in some cases, be deemed to be a resident alien (as opposed to a nonresident alien) by virtue of being present in the United States for at least 31 days in the calendar year and for an aggregate of at least 183 days during a three-year period ending in the current calendar year. Generally, for this purpose, all the days present in the current year, one-third of the days present in the immediately preceding year, and one-sixth of the days present in the second preceding year, are counted.

Resident aliens are generally subject to U.S. federal income tax as if they were U.S. citizens. Individuals who are uncertain of their status as resident or nonresident aliens for U.S. federal income tax purposes are urged to consult their own tax advisors regarding the U.S. federal income tax consequences of the ownership or disposition of our common stock.

PERSONS CONSIDERING THE PURCHASE OF OUR COMMON STOCK OR PRE-FUNDED WARRANTS PURSUANT TO THIS OFFERING SHOULD CONSULT THEIR OWN TAX ADVISORS CONCERNING THE U.S. FEDERAL INCOME TAX CONSEQUENCES OF ACQUIRING, OWNING AND DISPOSING OF OUR COMMON STOCK AND PRE-FUNDED WARRANTS IN LIGHT OF THEIR PARTICULAR SITUATIONS AS WELL AS ANY CONSEQUENCES ARISING UNDER THE LAWS OF ANY OTHER TAXING JURISDICTION, INCLUDING ANY STATE, LOCAL OR NON-U.S. TAX CONSEQUENCES OR ANY U.S. FEDERAL NON-INCOME TAX CONSEQUENCES, AND THE POSSIBLE APPLICATION OF TAX TREATIES.

Characterization of the Pre-Funded Warrants for Tax Purposes

Although the characterization of the pre-funded warrants for U.S. federal income tax purposes is not entirely clear, because the exercise price of the pre-funded warrants is a nominal amount, we expect to treat the pre-funded warrants as our common stock for U.S. federal income tax purposes and a holder of pre-funded warrants should generally be taxed in the same manner as a holder of common stock as described below. Accordingly, for U.S. federal income tax purposes, no gain or loss should be recognized upon the exercise of a pre-funded warrant, and upon exercise, the holding period of the share of common stock received should include the holding period of the pre-funded warrant. Similarly, the tax basis of a share of common stock received upon exercise of a pre-funded warrant should include the tax basis of the pre-funded warrant increased by the exercise price of \$0.0001 per share. The balance of this discussion generally assumes that the characterization described above is respected for U.S. federal income tax purposes, and the discussion below, to the extent it pertains to our common stock, is generally intended to also pertain to the pre-funded warrants.

Our position with respect to the characterization of pre-funded warrants is not binding on the IRS and the IRS may treat the pre-funded warrants as warrants to acquire our common stock and, if so, the amount and character of your gain with respect to an investment in our pre-funded warrants could change. You should consult your tax advisor regarding the characterization of pre-funded warrants for U.S. federal income tax purposes, and the consequences to you of an investment in the pre-funded warrants based on your own particular facts and circumstances.

Tax Consequences to U.S. Holders

Distributions on Common Stock

As stated under “Dividend Policy,” we do not expect to make distributions on our common stock in the foreseeable future. In the event that we do make distributions of cash or other property, distributions paid on common stock or pre-funded warrants will be treated as a dividend to the extent paid out of our current or accumulated earnings and profits, and will be includible in your income as ordinary income when received. However, with respect to dividends received by individuals, such dividends are generally taxed at the lower applicable long-term capital gains rates, provided certain holding period requirements are satisfied. Distributions in excess of our current and accumulated earnings and profits will be treated as a return of capital to the extent of a U.S. Holder’s tax basis in the common stock (or pre-funded warrant) and thereafter as capital gain from the sale or exchange of such common stock (or pre-funded warrant). The tax treatment of such gain is further described in “—Sale or Other Disposition of Common Stock or Pre-Funded Warrants” below. Dividends received by a corporation may be eligible for a dividends received deduction, subject to applicable limitations. Any such distributions will also be subject to the discussions below under the section titled “—Information Reporting and Backup Withholding.”

A holder of a pre-funded warrant should consult its tax advisor regarding the tax treatment of any distribution with respect to such pre-funded warrant that is held in abeyance in connection with any applicable limitation on the holder’s beneficial ownership of our common stock.

Sale or Other Disposition of Common Stock or Pre-Funded Warrants

For U.S. federal income tax purposes, gain or loss realized on the sale or other disposition of common stock or pre-funded warrants will be capital gain or loss, and will be long-term capital gain or loss if you have held the common stock or pre-funded warrants for more than one year. The amount of the gain or loss will equal the difference between your tax basis in the common stock or pre-funded warrants disposed of and the amount realized on the disposition. Long-term capital gains recognized by non-corporate U.S. Holders will be subject to reduced tax rates. The deductibility of capital losses is subject to limitations.

Certain Adjustments to the Pre-Funded Warrants

The exercise terms of the pre-funded warrants may be adjusted under certain circumstances. Under Section 305 of the Code, an adjustment to the number of shares of common stock that will be issued on the exercise of the pre-funded warrants, or an adjustment to the exercise price of the pre-funded warrants, may be treated as a constructive distribution to a U.S. Holder of the pre-funded warrants if, and to the extent that, such adjustment has the effect of increasing such U.S. Holder’s proportionate interest in our “earnings and profits” or assets, depending on the circumstances of such adjustment (for example, if such adjustment is to compensate for a distribution of cash or other property to our shareholders). Adjustments to the exercise price of pre-funded warrants or number of shares of common stock that will be issued on the exercise of a pre-funded warrant that are made pursuant to a bona fide reasonable adjustment formula that has the effect of preventing dilution of the interest of the U.S. Holder of the pre-funded warrants generally should not be considered to result in a constructive distribution. Such constructive distribution would be treated as a dividend, return of capital or capital gain as described under the heading “U.S. Holder—Distributions on Common Stock” above. Any such constructive distribution would be taxable whether or not there is an actual distribution of cash or other property.

Information Reporting and Backup Withholding

Information reporting requirements generally will apply to payments of dividends on our common stock, constructive dividends on our pre-funded warrants, and gross proceeds on the sale or other disposition of our common stock and pre-funded warrants, unless the U.S. Holder is an exempt recipient (such as a corporation). Backup withholding (currently at a 24% rate) will apply to those payments if the U.S. Holder fails to provide its

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correct taxpayer identification number, or certification of exempt status, or if the U.S. Holder is notified by the IRS that it has failed to report in full payments of interest and dividend income. Any amounts withheld under the backup withholding rules will be allowed as a refund or a credit against a U.S. Holder's U.S. federal income tax liability provided the required information is furnished timely to the IRS.

Tax Consequences to Non-U.S. Holders

For purposes of this discussion, a Non-U.S. Holder is a beneficial owner of our common stock or pre-funded warrants that, for U.S. federal income tax purposes, is neither a U.S. Holder (as defined above) nor a partnership or other pass-through entity. If you are not a Non-U.S. Holder, this section does not apply to you.

Distributions on Common Stock

As stated under "Dividend Policy," we do not expect to make any distributions on our common stock in the foreseeable future. If we do make distributions on our common stock or pre-funded warrants, however, such distributions made to a Non-U.S. Holder will constitute dividends for U.S. tax purposes to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Distributions in excess of our current and accumulated earnings and profits will constitute a return of capital that is applied against and reduces, but not below zero, a Non-U.S. Holder's adjusted tax basis in our common stock (or pre-funded warrants). Any remaining excess will be treated as gain realized as described below under the section titled "—Sale or Other Disposition of Common Stock and Pre-Funded Warrants."

Any distribution on our common stock or pre-funded warrants that is treated as a dividend paid to a Non-U.S. Holder that is not effectively connected with the holder's conduct of a trade or business in the United States will generally be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and the Non-U.S. Holder's country of residence. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide the applicable withholding agent with a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. Such form must be provided prior to the payment of dividends and must be updated periodically. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent may then be required to provide certification to the applicable withholding agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. withholding tax under an income tax treaty, you should consult with your own tax advisor to determine if you are able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that the holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if shares of our common stock are held through a financial institution or other agent, to the applicable withholding agent). In general, such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular graduated rates applicable to U.S. persons, unless a specific treaty exemption applies. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments.

See also the section below titled "—Foreign Accounts" for additional withholding rules that may apply to dividends paid to certain foreign financial institutions or non-financial foreign entities.

Sale or Other Disposition of Common Stock and Pre-Funded Warrants

Subject to the discussion below under the sections titled “—Information Reporting and Backup Withholding” and “—Foreign Accounts,” a Non-U.S. Holder generally will not be subject to U.S. federal income or withholding tax with respect to gain realized on a sale or other disposition of our common stock or pre-funded warrants unless (a) the gain is effectively connected with a trade or business of the holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that the holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a “United States real property holding corporation” within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or the holder’s holding period in the common stock or pre-funded warrants.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at the regular graduated U.S. federal income tax rates applicable to U.S. persons, unless a specific treaty exemption applies. Corporate Non-U.S. Holders described in (a) above may also be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by certain U.S. source capital losses (even though you are not considered a resident of the United States), provided you have timely filed U.S. federal income tax returns with respect to such losses. With respect to (c) above, in general, we would be a U.S. real property holding corporation if interests in U.S. real estate comprised (by fair market value) at least half of our worldwide real property interests plus our other assets used or held for use in a trade or business. We believe that we are not, and do not anticipate becoming, a U.S. real property holding corporation. However, there can be no assurance that we will not become a U.S. real property holding corporation in the future.

Certain Adjustments to the Pre-Funded Warrants

The exercise terms of the pre-funded warrants may be adjusted under certain circumstances. Under Section 305 of the Code, an adjustment to the number of shares of common stock that will be issued on the exercise of the pre-funded warrants, or an adjustment to the exercise price of the pre-funded warrants, may be treated as a constructive distribution to a Non-U.S. Holder of the pre-funded warrants if, and to the extent that, such adjustment has the effect of increasing such Non-U.S. Holder’s proportionate interest in our “earnings and profits” or assets, depending on the circumstances of such adjustment (for example, if such adjustment is to compensate for a distribution of cash or other property to our shareholders). Adjustments to the exercise price of pre-funded warrants or number of shares of common stock that will be issued on the exercise of a pre-funded warrant that are made pursuant to a bona fide reasonable adjustment formula that has the effect of preventing dilution of the interest of the Non-U.S. Holder of the pre-funded warrants generally should not be considered to result in a constructive distribution. Such constructive distribution would be treated as a dividend, return of capital or capital gain as described under the heading “Tax Consequences to Non-U.S. Holders—Distributions on Common Stock” above. Any such constructive distribution would be taxable whether or not there is an actual distribution of cash or other property. Any distribution treated as a dividend would generally be subject to 30% U.S. withholding tax, as described in “—Distributions on Common Stock” above.

U.S. Federal Estate Tax

The estates of nonresident alien individuals generally are subject to U.S. federal estate tax on property with a U.S. situs. Because we are a U.S. corporation, our common stock and pre-funded warrants will be U.S. situs property and, therefore, will be included in the taxable estate of a nonresident alien decedent, unless an applicable estate tax treaty between the United States and the decedent’s country of residence provides otherwise. The terms “resident” and “nonresident” are defined differently for U.S. federal estate tax purposes than for U.S. federal income tax purposes. Investors are urged to consult their own tax advisors regarding the U.S. federal estate tax consequences of the ownership or disposition of our common stock or pre-funded warrants.

Information Reporting and Backup Withholding

Generally, we or certain financial middlemen must report information to the IRS with respect to any dividends we pay on our common stock or any constructive dividends deemed paid on the pre-funded warrants including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable, or otherwise establishes an exemption, provided that the applicable withholding agent does not have actual knowledge or reason to know the holder is a U.S. person.

Under current U.S. federal income tax law, U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock or pre-funded warrants effected by or through a U.S. office of any broker, U.S. or non-U.S., unless the Non-U.S. Holder provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable, or otherwise meets documentary evidence requirements for establishing non-U.S. person status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Backup withholding is not an additional tax. If backup withholding is applied to you, you should consult with your own tax advisor to determine whether you have overpaid your U.S. federal income tax, and whether you are able to obtain a tax refund or credit of the overpaid amount.

Foreign Accounts

In addition to, and separately from the withholding rules described above, U.S. federal withholding taxes may apply under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments, including dividends to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends paid in respect of our common stock or pre-funded warrants, constructive distributions deemed paid with respect to the pre-funded warrants and the gross proceeds of the disposition on our common stock or pre-funded warrants paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution agrees to undertake certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. The 30% federal withholding tax described in this paragraph cannot be reduced under an income tax treaty with the United States. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States-owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

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The Treasury Secretary has issued proposed regulations providing that the withholding provisions under FATCA do not apply with respect to payment of gross proceeds from a sale or other disposition of our notes or common stock, which may be relied upon by taxpayers until final regulations are issued. Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock or pre-funded warrants.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK AND PRE-FUNDED WARRANTS, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW, AS WELL AS TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL, NON-U.S. OR U.S. FEDERAL NON-INCOME TAX LAWS SUCH AS ESTATE AND GIFT TAX.

UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC is acting as representative, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares of common stock and pre-funded warrants indicated below:

Name	Number of Shares of Common Stock	Number of Pre-Funded Warrants
Morgan Stanley & Co. LLC	4,496,744	12,895,256
Total	<u>4,496,744</u>	<u>12,895,256</u>

The underwriters and the representative are collectively referred to as the “underwriters” and the “representative,” respectively. The underwriters are offering the shares of common stock and pre-funded warrants subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of voting and non-voting common stock and pre-funded warrants offered by this prospectus supplement are subject to certain conditions precedent. The underwriters are obligated to take and pay for all of the shares of common stock and pre-funded warrants offered by this prospectus supplement if any such shares and pre-funded warrants are taken. However, the underwriters are not required to take or pay for the shares of common stock, including the number of shares underlying the pre-funded warrants covered by the underwriters’ option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock and pre-funded warrants directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of \$0.207 per share of common stock or per pre-funded warrant under the public offering price. After the initial offering of the shares of common stock and pre-funded warrants, the offering price and other selling terms may from time to time be varied by the representative.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 2,608,800 additional shares of voting common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. The number of shares subject to the underwriters’ option equals 15% of the total number of shares of common stock plus the number of shares underlying the pre-funded warrants. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter’s name in the preceding table bears to the total number of shares of common stock and pre-funded warrants listed next to the names of all underwriters in the preceding table.

To the extent shares of common stock offered hereby are purchased by existing stockholders that hold shares of our non-voting common stock, such shares may initially be issued in the form of non-voting common stock that will be convertible into an equivalent number of shares of our voting common stock.

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The following table shows the per share and pre-funded warrant total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 2,608,800 shares of voting common stock.

	Per Share of Common Stock	Per Pre-Funded Warrant	Total	
			No Exercise	Full Exercise
Public offering price	\$ 5.7500	\$ 5.7499	\$100,002,710	\$115,003,310
Underwriting discounts and commissions to be paid by us ⁽¹⁾ :	\$ 0.345	\$ 0.345	\$ 1,200,240	\$ 2,100,276
Proceeds, before expenses, to us ⁽¹⁾	\$ 5.4050	\$ 5.4049	\$ 98,802,470	\$112,903,034

(1) The underwriters will not receive any underwriting discounts or commissions on 2,317,787 shares of common stock and 11,595,256 pre-funded warrants that investment entities affiliated with our 5% stockholders affiliated with our directors have expressed an interest in purchasing.

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$272,000. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority of up to \$30,000.

Our common stock is listed on The Nasdaq Global Select Market under the trading symbol "PRLD". The non-voting common stock is not listed on any national securities exchange. We do not intend to list the pre-funded warrants on The Nasdaq Global Select Market, any other nationally recognized securities exchange or any other nationally recognized trading system.

We and all directors and officers and certain stockholders have agreed that, without the prior written consent of Morgan Stanley & Co. LLC, on behalf of the underwriters, we and they will not, and will not publicly disclose an intention to, during the period ending 90 days after the date of this prospectus supplement, or the restricted period:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or non-voting common stock or any securities convertible into or exercisable or exchangeable for shares of common stock or non-voting common stock;
- file any registration statement with the SEC relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock or non-voting common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock or non-voting common stock;

whether any such transaction described above is to be settled by delivery of common stock, non-voting common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of Morgan Stanley & Co. LLC on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

References to common stock in the following description refer to both voting and non-voting common stock. The restrictions described in the immediately preceding paragraph do not apply to our directors, officers and securityholders with respect to:

- transactions relating to shares of common stock or other securities acquired in the offering or in open market transactions after the completion of the offering, provided that no filing under Section 16(a) of

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the Exchange Act shall be required or shall be voluntarily made during the restricted period in connection with subsequent sales of common stock or other securities acquired in the offering or such open market transactions;

- transfers or dispositions of shares of common stock or any security convertible into or exercisable or exchangeable for common stock (i) as a bona fide gift or charitable contribution, (ii) by will or intestacy or to any member of the holder's immediate family or to a trust for the direct or indirect benefit of the holder and/or any member of the holder's immediate family, (iii) to any corporation, partnership, limited liability company or other business entity, all of the beneficial ownership interests of which, in each such case, are held by the holder or any member of the holder's immediate family, (iv) if the holder is an entity, to limited partners, members, shareholders or holders of similar equity interests in the holder, or (v) if the holder is an entity, to another corporation, partnership, limited liability company, trust or other business entity that is an affiliate (as defined in Rule 405 promulgated under the Securities Act) of the holder, or to any investment fund or other entity controlled or managed by the holder or affiliated with the holder; provided that, in the case of any transfer or distribution pursuant to this clause, (A) each transferee, donee or distributee shall sign and deliver a substantially similar lock-up agreement and (B) no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of common stock or any securities convertible into or exercisable or exchangeable for common stock shall be required or shall be voluntarily made during the restricted period (other than, in the case of a transfer or other disposition pursuant to clause (i) above, a Form 4 or clause (ii) above, a Form 5 in each case required to be filed under the Exchange Act if the holder is subject to Section 16 reporting with respect to Prelude under the Exchange Act; any such filing will indicate by footnote disclosure or otherwise the nature of the transfer or disposition); and provided further that any such transfer pursuant to this clause shall not involve a transfer or distribution for value;
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for shares of common stock by operation of law pursuant to a qualified domestic order or other court order or in connection with a divorce settlement; provided that (i) any filing under Section 16(a) of the Exchange Act made during the restricted period shall clearly indicate in the footnotes thereto that (A) the filing relates to the circumstances described in this clause and (B) no securities were sold by the holder, and (ii) the holder does not otherwise voluntarily effect any other public filing or report regarding such transfers during the restricted period;
- (i) the exercise of options or other similar awards or the vesting or settlement of awards granted pursuant to our equity incentive plans as described in this prospectus supplement and outstanding on the date of the underwriting agreement (including the delivery and receipt of shares of common stock, other awards or any securities convertible into or exercisable or exchangeable for shares of common stock in connection with such exercise, vesting or settlement), or (ii) the transfer or disposition of shares of common stock or any securities convertible into shares of common stock by the holder to the company (or the purchase and cancellation of the same by the company) upon a vesting or settlement event of our securities or upon the exercise of options to purchase our securities on a "cashless" or "net exercise" basis solely to the extent permitted by the instruments representing such options pursuant to our equity incentive plans as described in this prospectus supplement and solely to cover withholding tax obligations in connection with such transaction and any transfer to the company for the payment of taxes as a result of such transaction, provided that (A) the shares of common stock received upon the exercise or settlement of the option are subject to the same restrictions, (B) no public disclosure or filing under Section 16(a) of the Exchange Act shall be voluntarily made during the restricted period and (C) to the extent a filing under Section 16(a) of the Exchange Act is required during the restricted period as a result of transfers in this clause, it shall clearly indicate that the filing relates to the circumstances described in this clause;
- transfers to the company pursuant to the repurchase of shares of common stock in connection with the termination of the holder's employment with the company or other service relationship with the company pursuant to contractual agreements with the company as in effect as of the date of this prospectus supplement, provided that no public disclosure or filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made during the restricted period;

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- transactions in connection with the conversion of non-voting common stock to voting common stock, provided that any such shares of voting common stock received upon such conversion or reclassification remain subject to the same restrictions;
- facilitating the establishment of a trading plan on behalf of a stockholder, officer or director pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required of or voluntarily made by or on behalf of the holder or the company regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period; or
- transfers pursuant to a bona fide third-party tender offer for all outstanding shares of common stock or securities convertible into or exercisable or exchangeable for shares of common stock, merger, amalgamation, consolidation or other similar transaction approved by our board of directors and made to all holders of our securities involving a “change of control” (as defined in the lock-up agreement) of the company (including, without limitation, the entering into any lock-up, voting or similar agreement pursuant to which the holder may agree to transfer, sell, tender or otherwise dispose of shares of common stock or other such securities in connection with such transaction, or vote any shares of common stock or other such securities in favor of any such transaction); provided that in the event that such tender offer, merger, amalgamation, consolidation or other such transaction is not completed, such securities held by the holder shall remain subject to the same restrictions.

The restrictions on transfers or other dispositions by us described above do not apply to:

- the securities to be sold in this offering, including the issuance by us of shares of common stock upon the exercise of the prefunded warrants;
- the issuance by us of shares of common stock or securities convertible into or exercisable for shares of common stock upon the exercise of an option or warrant or the conversion of a security outstanding on the date of this prospectus supplement and described herein;
- the issuance by us of shares of common stock or non-voting common stock upon the exchange of any security exchangeable therefor or the conversion of any security convertible therefor pursuant to a contractual arrangement or other right described herein, provided that each recipient of such issuance executes and delivers a lock-up agreement;
- the issuance by us of shares of voting common stock in connection with a conversion of non-voting common stock to voting common stock, provided that any such shares of voting common stock received upon such conversion or reclassification shall be subject to the lock-up agreement;
- facilitating the establishment of a trading plan on behalf of one of our shareholders, officers or directors pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for the transfer of common stock during the restricted period and, to the extent a public announcement or filing under the Exchange Act is required of or voluntarily made by us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period;
- the grant of any options to purchase shares of common stock or other awards granted under a stock incentive plan or stock purchase plan described in this prospectus supplement, and the issuance by us of shares of common stock upon the exercise thereof, provided that each recipient of such grant executes and delivers a lock-up agreement;
- our filing of any registration statement on Form S-8 or a successor form relating to the shares of common stock granted pursuant to or reserved for issuance under a stock incentive plan or stock purchase plan described in this prospectus supplement;

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- shares of common stock or other securities issued in connection with a transaction with an unaffiliated third party that includes a debt financing or a bona fide commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements, or intellectual property license agreements) or any acquisition of assets or acquisition of not less than a majority or controlling portion of the equity of another entity, provided that (1) the aggregate number of shares issued does not exceed 5% of the total number of outstanding shares of our common stock immediately following the closing of this offering (giving effect to the shares of common stock issuable upon exercise of the pre-funded warrants) and (2) the recipient of any such securities during the restricted period enters into a lock-up agreement; or
- shares of common stock in connection with sales under the Sale Agreement, provided no sales shall be made under the Sale Agreement until the earlier of (i) the exercise in full by the underwriters of their option to purchase additional shares of voting common stock or (ii) 30 days after the date of the underwriting agreement.

Morgan Stanley & Co. LLC, in its sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representative may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representative to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses. For example, one of the underwriters also served as an underwriter in our initial public offering in September 2020 and in our follow-on offering in January 2021.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related

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derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Investment entities affiliated with our 5% stockholders affiliated with our directors have expressed an interest in purchasing an aggregate of 2,317,787 shares of common stock and 11,595,256 pre-funded warrants in this offering at the public offering price. The underwriter will not receive any underwriting discounts or commissions on securities purchased by such investment entities.

Selling Restrictions

Notice to Prospective Investors in Canada

The shares of common stock and pre-funded warrant shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of shares of common stock or pre-funded warrant shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement or the accompanying prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant State), no securities have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the securities which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that securities may be offered to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;
- to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation), subject to obtaining the prior consent of the underwriter for any such offer; or
- in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of securities shall require us or the underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

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For the purposes of this provision, the expression an “offer to the public” in relation to any securities in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase or subscribe for any securities, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129, as amended.

Notice to Prospective Investors in the United Kingdom

No securities have been offered or will be offered pursuant to the offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the securities which has been approved by the Financial Conduct Authority, except that the securities may be offered to the public in the United Kingdom at any time under the following exemptions under the UK Prospectus Regulation:

- to any legal entity which is a qualified investor as defined under Article 2 of the UK Prospectus Regulation;
- to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the UK Prospectus Regulation), subject to obtaining the prior consent of the underwriter for any such offer;
- in any other circumstances falling within Section 86 of the Financial Services and Markets Act 2000 (the FSMA),

provided that no such offer of the securities shall require us or the underwriter to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation. For the purposes of this provision, the expression an “offer to the public” in relation to the securities in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase or subscribe for any securities and the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018 (the UK Prospectus Regulation).

Any invitation or inducement to engage in investment activity (within the meaning of Section 21 of the FSMA) in connection with the issue or sale of any securities may only be communicated or caused to be communicated in circumstances in which Section 21(1) of the FSMA does not apply to the Company. Each purchaser of securities must comply with all applicable provisions of the FSMA and the Financial Services Act 2012 with respect to anything done by it in relation to any securities in, from or otherwise involving the United Kingdom.

This prospectus supplement is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors as defined in the UK Prospectus Regulation that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (as amended, the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order or (iii) persons to whom an invitation or inducement to engage in investment activity (within the meaning of section 21 of the FSMA) in connection with the issue or sale of any securities may otherwise lawfully be communicated or caused to be communicated (each such person being referred to as a “relevant person”). This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this prospectus supplement or any of its contents.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this prospectus supplement or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this prospectus supplement relates to may be made or taken exclusively by relevant persons.

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Notice to Prospective Investors in Hong Kong

The shares of common stock and pre-funded warrant shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) (the SFO) of Hong Kong and any rules made thereunder; or (b) in other circumstances which do not result in the document being a “prospectus” as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong (the CO) or which do not constitute an offer to the public within the meaning of the CO. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the SFO and any rules made thereunder.

Notice to Prospective Investors in Japan

The shares of common stock and pre-funded warrant shares have not been and will not be registered pursuant to Article 4, Paragraph 1 of the Financial Instruments and Exchange Act. Accordingly, none of the shares of common stock or pre-funded warrant shares nor any interest therein may be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any “resident” of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan in effect at the relevant time.

For Qualified Institutional Investors, or QII

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a “QII only private placement” or a “QII only secondary distribution” (each as described in Paragraph 1, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred to QIIs.

For Non-QII Investors

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a “small number private placement” or a “small number private secondary distribution” (each as is described in Paragraph 4, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred en bloc without subdivision to a single investor.

Singapore Securities and Futures Act Production Classification

Solely for the purposes of its obligations pursuant to sections 309B(1)(a) and 309B(1)(c) of the Securities and Futures Act (Chapter 289 of Singapore) (the SFA), we have determined, and hereby notify all relevant persons (as defined in Section 309A of the SFA) that the shares of common stock and pre-funded warrants are “prescribed capital markets products” (as defined in the Securities and Futures (Capital Markets Products) Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04-N12: Notice on the Sale of Investment Products and MAS Notice FAA-N16: Notice on Recommendations on Investment Products).

Notice to Prospective Investors in Switzerland

The shares of common stock and pre-funded warrant shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange (SIX) or on any other stock exchange or regulated trading facility

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in Switzerland. This prospectus supplement does not constitute a prospectus within the meaning of, and has been prepared without regard to, the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus supplement nor any other offering or marketing material relating to the shares of common stock and pre-funded warrant shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus supplement nor any other offering or marketing material relating to the offering, the Company, the shares of common stock or the pre-funded warrant shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus supplement will not be filed with, and the offer of shares of common stock and pre-funded warrant shares will not be supervised by, the Swiss Financial Market Supervisory Authority, and the offer of these securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes (CISA). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Markets Rules 2012 of the Dubai Financial Services Authority, or DFSA. This prospectus supplement is intended for distribution only to persons of a type specified in the Markets Rules 2012 of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for this prospectus supplement. The securities to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the securities offered should conduct their own due diligence on the securities. If you do not understand the contents of this prospectus supplement, you should consult an authorized financial advisor.

In relation to its use in the DIFC, this prospectus supplement is strictly private and confidential and is being distributed to a limited number of investors and must not be provided to any person other than the original recipient and may not be reproduced or used for any other purpose. The interests in the securities may not be offered or sold directly or indirectly to the public in the DIFC.

Notice to Prospective Investors in Australia

This prospectus supplement and the accompanying prospectus:

- does not constitute a disclosure document under Chapter 6D.2 of the Corporations Act 2001 (Cth) (the Corporations Act);
- has not been, and will not be, lodged with the Australian Securities and Investments Commission (ASIC), as a disclosure document for the purposes of the Corporations Act, and does not purport to include the information required of a disclosure document under Chapter 6D.2 of the Corporations Act; and
- may only be provided in Australia to select investors who are able to demonstrate that they fall within one or more of the categories of investors, or Exempt Investors, available under section 708 of the Corporations Act.

The shares of common stock and pre-funded warrant shares may not be directly or indirectly offered for subscription or purchased or sold, and no invitations to subscribe for or buy the shares of common stock or pre-funded warrant shares may be issued, and no draft or definitive offering memorandum, advertisement or other offering material relating to any securities may be distributed in Australia, except where disclosure to

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investors is not required under Chapter 6D of the Corporations Act or is otherwise in compliance with all applicable Australian laws and regulations. By submitting an application for the securities, you represent and warrant to us that you are an Exempt Investor.

As any offer of shares of common stock and pre-funded warrant shares under this prospectus supplement will be made without disclosure in Australia under Chapter 6D.2 of the Corporations Act, the offer of those securities for resale in Australia within 12 months may, under section 707 of the Corporations Act, require disclosure to investors under Chapter 6D.2 if none of the exemptions in section 708 applies to that resale. By applying for the shares you undertake to us that you will not, for a period of 12 months from the date of issue of the shares, offer, transfer, assign or otherwise alienate those securities to investors in Australia except in circumstances where disclosure to investors is not required under Chapter 6D.2 of the Corporations Act or where a compliant disclosure document is prepared and lodged with ASIC.

Notice to Prospective Investors in Israel

In the State of Israel this prospectus supplement shall not be regarded as an offer to the public to purchase common shares or pre-funded warrant shares under the Israeli Securities Law, 5728-1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728-1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions, or the Addressed Investors; or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728-1968, subject to certain conditions, or the "Qualified Investors." The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. We have not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728- 1968. We have not and will not distribute this prospectus supplement or make, distribute or direct an offer to subscribe for our common shares or pre-funded warrant shares to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728-1968. In particular, we may request, as a condition to be offered common shares and pre-funded warrant shares, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728-1968 and the regulations promulgated thereunder in connection with the offer to be issued common shares and pre-funded warrant shares; (iv) that the common shares and pre-funded warrant shares that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728-1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728-1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

LEGAL MATTERS

The validity of the common stock and pre-funded warrants offered hereby and certain legal matters in connection with this offering will be passed upon by Fenwick & West LLP, San Francisco, California. Cooley LLP, New York, New York is acting as counsel for the underwriter in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 (Registration No. 333-261019) under the Securities Act with respect to the shares of common stock offered hereby. This prospectus supplement, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits filed therewith. For further information about us and the shares of common stock offered hereby, reference is made to the accompanying prospectus and registration statement of which it is a part and the exhibits filed therewith. Statements contained in this prospectus supplement regarding the contents of any contract or any other document that is filed as an exhibit to the accompanying prospectus and the registration statement of which it is a part are not necessarily complete, and in each instance we refer you to the copy of such contract or other document filed as an exhibit to the registration statement or the exhibits to the reports or other documents incorporated by reference in this prospectus supplement for a copy of such contract or other document.

We are subject to the informational requirements of the Exchange Act and are required to file annual, quarterly and other reports, proxy statements and other information with the SEC. The SEC maintains an Internet site (<http://www.sec.gov>) that contains reports, proxy and information statements, and various other information about us.

Information about us is also available at our website at www.preludetx.com. However, the information on our website is not a part of this prospectus supplement and is not incorporated by reference into this prospectus supplement.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus supplement and the accompanying prospectus, and information we file later with the SEC will automatically update and supersede this information. A Current Report (or portion thereof) furnished, but not filed, on Form 8-K shall not be incorporated by reference into this prospectus supplement and the accompanying prospectus. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of shares of common stock made by this prospectus supplement and accompanying prospectus:

- Our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2022, filed with the SEC on March 15, 2023;
- Our Quarterly Report on [Form 10-Q](#) for the fiscal quarter ended March 31, 2023, filed with the SEC on May 8, 2023;
- Our Preliminary Proxy Statement on Schedule 14A, filed with the SEC on [April 18, 2023](#) and our Definitive Proxy Statement on Schedule 14A, filed with the SEC on [April 28, 2023](#) (but, in each case, only with respect to information required by Part III of our Annual Report on Form 10-K for the year ended December 31, 2022, which information shall update and supersede information included in Part III of our Annual Report on Form 10-K for the year ended December 31, 2022);
- Our Current Reports on Form 8-K filed with the SEC on [January 23, 2023](#), [March 15, 2023](#), [March 15, 2023](#) and [May 17, 2023](#); and
- The description of our common stock contained in our registration statement on [Form 8-A](#) filed with the SEC on September 16, 2020 under Section 12(b) of the Exchange Act, as the description therein has been updated and superseded by the description of our capital stock contained in [Exhibit 4.4](#) of our Annual Report on Form 10-K for the fiscal year ended December 31, 2022, as filed with the SEC on March 15, 2023, including any amendment or report filed for the purpose of updating such description.

We will furnish without charge to you, on written or oral request, a copy of any or all of such documents that has been incorporated herein by reference in this prospectus supplement (other than exhibits to such documents unless such exhibits are specifically incorporated by reference into the documents that this prospectus supplement incorporates). Written or oral requests for copies should be directed to Prelude Therapeutics Incorporated, Attn: Chief Legal Officer, 200 Powder Mill Road Wilmington, Delaware 19803, and our telephone number is (302) 467-1280. See the section of this prospectus supplement entitled “Where You Can Find More Information” for information concerning how to read and obtain copies of materials that we file with the SEC.

Any statement contained in this prospectus supplement, or in a document all or a portion of which is incorporated by reference, shall be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or any document incorporated by reference modifies or supersedes such statement. Any such statement so modified or superseded shall not, except as so modified or superseded, constitute a part of this prospectus supplement.

PROSPECTUS

\$400,000,000



Prelude Therapeutics Incorporated

**Common Stock, Preferred Stock,
Debt Securities, Warrants, Subscription Rights and Units**

**31,574,631 shares of Common Stock
Offered by the Selling Stockholders**

From time to time, we may offer up to \$400,000,000 aggregate dollar amount of shares of our common stock or preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities and/or units consisting of some or all of these securities, in any combination, together or separately, in one or more offerings, in amounts, at prices and on the terms that we will determine at the time of the offering and which will be set forth in a prospectus supplement and any related free writing prospectus. This prospectus describes the general manner in which those securities may be offered using this prospectus. We will specify in an accompanying prospectus supplement and any related free writing prospectus the terms of securities offered and the offering thereof and may also add, update or change information contained in this prospectus. The total amount of these securities will have an initial aggregate offering price of up to \$400,000,000.

In addition, this prospectus relates to the offer and sale from time to time of up to 31,574,631 shares of common stock under this prospectus by the selling stockholders identified in the "Selling Stockholders" section of this prospectus or their permitted transferees, pledgees, donees or other successors in interest. The selling stockholders or their permitted transferees, pledgees, donees or other successors in interest may sell the shares of common stock in a number of different ways and at varying prices. We provide more information about how the selling stockholders may sell the shares of common stock in the section of this prospectus titled "Selling Stockholders Plan of Distribution." We will not receive any of the proceeds from the sale of our common stock by the selling stockholders. We have paid or will pay the fees and expenses incident to the registration of the shares of common stock for sale by the selling stockholders. The selling stockholders will bear all discounts, concessions, commissions and stock transfer taxes, if any, attributable to its sales of shares.

You should read this prospectus, the information incorporated, or deemed to be incorporated, by reference in this prospectus, and any applicable prospectus supplement and related free writing prospectus carefully before you invest.

Our common stock is traded on The Nasdaq Global Select Market under the symbol "PRLD." On November 11, 2021, the last reported sales price for our common stock was \$16.76 per share. None of the other securities we may offer are currently traded on any securities exchange. The applicable prospectus supplement and any related free writing prospectus will contain information, where applicable, as to any other listing on The Nasdaq Global Select Market or any securities market or exchange of the securities covered by the prospectus supplement and any related free writing prospectus.

An investment in our securities involves a high degree of risk. You should carefully consider the information under the heading "[Risk Factors](#)" beginning on page 6 of this prospectus before investing in our securities.

Common stock, preferred stock, debt securities, warrants, subscription rights and/or units may be sold by us, or the selling stockholders to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any underwriters, dealers or agents are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, discounts or commissions, details regarding over-allotment options, if any, and the net proceeds to us will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

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

The date of this prospectus is November 24, 2021

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings, up to a total dollar amount of \$400,000,000, and the selling stockholders may sell up to 31,574,631 shares of our common stock from time to time in one or more offerings as described in this prospectus. We have provided to you in this prospectus a general description of the securities we may offer. Each time we, or the selling stockholders, sell securities under this shelf registration process, we, or the selling stockholders, will provide a prospectus supplement that will contain specific information about the terms of the offering. We, or the selling stockholders, may also add, update or change in the prospectus supplement any of the information contained in this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement; *provided* that, if any statement in one of these documents is inconsistent with a statement in another document having a later date - for example, a document incorporated by reference in this prospectus or any prospectus supplement - the statement in the document having the later date modifies or supersedes the earlier statement. You should read both this prospectus and any prospectus supplement together with additional information described under the heading “Where You Can Find More Information.”

Neither we, nor any agent, the selling stockholders, underwriter or dealer have authorized anyone to give you any information or to make any representation other than the information and representations contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We and any agent, the selling stockholders, underwriter or dealer take no responsibility for, and can provide no assurance as to the reliability of, any other information others may give you. You may not imply from the delivery of this prospectus and any applicable prospectus supplement, nor from a sale made under this prospectus and any applicable prospectus supplement, that our affairs are unchanged since the date of this prospectus and any applicable prospectus supplement or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus and any applicable prospectus supplement or any sale of a security. This prospectus and any applicable prospectus supplement may only be used where it is legal to sell the securities.

THIS PROSPECTUS MAY NOT BE USED TO OFFER AND SELL SECURITIES UNLESS IT IS ACCOMPANIED BY AN ADDITIONAL PROSPECTUS OR A PROSPECTUS SUPPLEMENT.

In this prospectus, unless the context otherwise requires, the terms “Prelude,” “Prelude Therapeutics,” the “Company,” “we,” “us,” and “our” refer to Prelude Therapeutics Incorporated, a Delaware corporation.

PROSPECTUS SUMMARY

This summary highlights information contained in other parts of this prospectus or incorporated by reference in this prospectus from our [Annual Report on Form 10-K for the year ended December 31, 2020](#), our [Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2021](#) and our other filings with the SEC listed below under the heading “Incorporation of Information by Reference.” This summary may not contain all the information that you should consider before investing in securities. You should read the entire prospectus and the information incorporated by reference in this prospectus carefully, including “Risk Factors” and the financial data and related notes and other information incorporated by reference, before making an investment decision. See “Forward-Looking Statements.”

Our Company

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 these programs into clinical development. In addition, we have three unique programs in various stages of preclinical development that we plan to advance into clinical development beginning in 2021.

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

Our lead product candidates are designed to be oral, potent and selective inhibitors of protein arginine methyltransferase 5, or PRMT5. The potency and selectivity of our product candidates is supported by preclinical data demonstrating nanomolar inhibition of PRMT5 and no inhibition of related enzymes at 1,000 times higher concentration of our product candidates. Updated data from the dose escalation phase of the ongoing Phase 1 trial of PRT543 was presented at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics held October 7, 2021 through October 10, 2021. As of an August 6, 2021 data cutoff date, the dose escalation portion of the ongoing Phase 1 trial of PRT543 enrolled a total of 49 patients across 18 unselected advanced solid tumors and lymphoma. Patients enrolled received an average of three prior lines of therapy. PRT543 demonstrated target engagement and inhibition of PRMT5 functional activity as evidenced by a 69% reduction in serum symmetric dimethylarginine, or sDMA, at a dose of 45 mg/5x per week. In addition, PRT543 demonstrated signs of preliminary clinical activity, including a durable complete response, or CR, maintained for over 18 months in a patient with HRD+ ovarian cancer who remains on treatment and prolonged stable disease, or SD, persisting for over six months in five patients, including four patients with ACC and one patient with uveal melanoma. A complete response is defined as the disappearance of all target lesions. PRT543 was generally well tolerated: the most common grade 3 or higher treatment-related adverse events, or AE,

occurring in at least 5% of patients were thrombocytopenia (27%) and anemia (12%), both of which were reversible upon treatment interruption. Patients were largely able to remain on therapy with few AE-related dose interruptions (27%), reductions (22%), or discontinuations (4%).

Patient enrollment is continuing in specific biomarker-selected solid tumor and hematologic malignancy expansion cohorts. We anticipate presenting data from the expansion cohorts of the trial at medical meetings throughout 2022.

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. Updated data from the dose escalation phase of the ongoing Phase 1 trial of PRT811 was presented at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics held October 7, 2021 through October 10, 2021. As of an August 13, 2021 data cutoff date, the dose escalation portion of the ongoing Phase 1 trial of PRT811 enrolled a total of 45 patients, including 27 patients across 16 unselected advanced solid tumors and 18 patients with high-grade gliomas, including 17 patients with glioblastoma multiforme, or GBM. PRT811 demonstrated dose dependent inhibition of PRMT5 activity as evidenced by an 83% reduction in serum sDMA at a dose of 600 mg daily (QD). In addition, PRT811 demonstrated signs of preliminary clinical activity, including an IDH1 mutated GBM patient who experienced a partial response, or PR, that evolved into a durable CR for more than 13 months and remains on treatment. In addition, a patient with splicing-mutant, or SF3B1, uveal melanoma demonstrated SD for more than six months with a 25% tumor regression and remains on treatment. At a post data-cutoff on September 20, 2021, one additional patient (800 mg QD) with SF3B1 uveal melanoma had an unconfirmed PR and 47% decrease in target lesion, and a patient with triple negative breast cancer (800 mg QD) demonstrated a 27% decrease in target lesions. Both patients continue treatment. PRT811 was generally well-tolerated; the most common grade 3 or higher treatment-related AE was thrombocytopenia (7%), which was reversible upon treatment interruption. Patients were largely able to remain on therapy with few AE-related dose interruptions (13%), reductions (4%), or discontinuations (3%).

The study remains ongoing, and the Company expects to commence enrollment in the expansion portion of the trial in the fourth quarter of 2021. Data from the expansion cohorts are expected to be presented at medical meetings throughout 2022.

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 dose escalation portion of a Phase 1 open-label, multicenter clinical trial for the oral formulation of PRT1419. We expect to add dose expansion and combination cohorts to the Phase 1 clinical trial in the second half of 2021. Additionally, in March 2021, the FDA cleared our IND for an intravenous, or IV, formulation of PRT1419. The Phase 1 trial of the IV formulation of PRT1419, which leverages the optimized physicochemical properties of PRT1419, is now underway in patients with solid tumors.

We recently received clearance for an IND application for our fourth clinical candidate, PRT2527. We remain on track to initiate a clinical trial for PRT2527 by year end.

The Securities We May Offer

With this prospectus, we may offer common stock, preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities, and/or units consisting of some or all of these securities in any combination. The

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aggregate offering price of securities that we offer with this prospectus will not exceed \$400,000,000. Each time we offer securities with this prospectus, we will provide offerees with a prospectus supplement that will contain the specific terms of the securities being offered. The following is a summary of the securities we may offer with this prospectus.

Common Stock

We may offer shares of our common stock, par value \$0.0001 per share. We have two classes of common stock: the voting common stock and the non-voting common stock. For a description of the rights of the voting common stock and non-voting common stock, please see “Description of Capital Stock” beginning on page 18 of this prospectus. Unless otherwise noted, all references in this prospectus to our “common stock” refer to our voting common stock. The non-voting common stock is not listed for trading on any securities exchange.

Preferred Stock

We may offer shares of our preferred stock, par value \$0.0001 per share, in one or more series. Our board of directors or a committee designated by the board will determine the dividend, voting, conversion and other rights of the series of shares of preferred stock being offered. Each series of preferred stock will be more fully described in the particular prospectus supplement that will accompany this prospectus, including redemption provisions, rights in the event of our liquidation, dissolution or the winding up, voting rights and rights to convert into common stock.

Debt Securities

We may offer general obligations, which may be secured or unsecured, senior or subordinated and convertible into shares of our common stock or preferred stock. In this prospectus, we refer to the senior debt securities and the subordinated debt securities together as the “debt securities.” Our board of directors will determine the terms of each series of debt securities being offered.

We will issue the debt securities under an indenture between us and a trustee. In this document, we have summarized general features of the debt securities from the indenture. We encourage you to read the indenture, which is an exhibit to the registration statement of which this prospectus is a part.

Warrants

We may offer warrants for the purchase of debt securities, shares of preferred stock or shares of common stock. We may issue warrants independently or together with other securities. Our board of directors will determine the terms of the warrants.

Subscription Rights

We may offer subscription rights for the purchase of common stock, preferred stock or debt securities. We may issue subscription rights independently or together with other securities. Our board of directors will determine the terms of the subscription rights.

Units

We may offer units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the related prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

* * *

We were formed under the laws of the State of Delaware in February 2016. Our principal executive offices are located at 200 Powder Mill Road, Wilmington, Delaware, 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 securities.

RISK FACTORS

An investment in our securities involves a high degree of risk. The prospectus supplement applicable to each offering of securities will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading “Risk Factors” in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under Part II, Item 1A, “Risk Factors,” in our [Quarterly Report on Form 10-Q for the quarter ended September 30, 2021](#), which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

FORWARD-LOOKING STATEMENTS

This prospectus and documents incorporated herein by reference contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events.

Such statements include, but are not limited to, statements regarding expectations and intentions, costs and expenses, outcome of contingencies, financial condition, results of operations, liquidity, objectives of management, debt financing, our future results of operations and financial position, the impact of the COVID-19 pandemic, business strategies, market size, potential growth opportunities, clinical development activities, efficacy and safety profile of our product candidates, timing and results of our pre-clinical studies and clinical trials, the receipt and timing of potential regulatory designations, our ability to maintain and recognize the benefits of certain designations received by product candidates, the achievement of clinical and commercial milestones, the advancement of our technologies and our proprietary product candidates, the successful achievement of the goals of our collaborations, the advancement of the product candidates that are the subjects of these collaborations, the approvals and commercialization of product candidates and other statements that are not historical facts. You can find many of these statements by looking for words like “believes,” “expects,” “anticipates,” “estimates,” “may,” “might,” “should,” “will,” “could,” “plan,” “intend,” “project,” “seek” or similar expressions in this prospectus, in documents incorporated by reference into this prospectus or any free writing prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in Part II, Item 1A, “Risk Factors,” in [Quarterly Report on Form 10-Q for the quarter ended September 30, 2021](#), as well as those discussed in this prospectus, the documents incorporated by reference into this prospectus and any free writing prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this prospectus or, in the case of documents referred to or incorporated by reference, the date of those documents.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act with respect to the securities offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement, the exhibits filed therewith or the documents incorporated by reference therein. For further information about us and the securities offered hereby, reference is made to the registration statement, the exhibits filed therewith and the documents incorporated by reference therein. Statements contained in this prospectus regarding the contents of any contract or any other document that is filed as an exhibit to the registration statement are not necessarily complete, and in each instance, we refer you to the copy of such contract or other document filed as an exhibit to the registration statement.

We are subject to the informational requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act and are required to file annual, quarterly and other reports, proxy statements and other information with the SEC. The SEC maintains an Internet site (<http://www.sec.gov>) that contains reports, proxy and information statements, and various other information about us. You may also inspect the documents described herein at our principal executive offices, 200 Powder Mill Road, Wilmington, Delaware, 19803, during normal business hours.

Information about us is also available at our website at <http://www.preludetx.com>. However, the information on our website is not a part of this prospectus and is not incorporated by reference into this prospectus.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information we file later with the SEC will automatically update and supersede this information. A Current Report (or portion thereof) furnished, but not filed, on Form 8-K shall not be incorporated by reference into this prospectus. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2020, filed with the SEC on March 16, 2021;
- our Quarterly Reports on Form 10-Q for the quarters ended [March 31, 2021](#), [June 30, 2021](#) and [September 30, 2021](#), filed with the SEC on May 11, 2021, August 12, 2021 and November 12, 2021, respectively;
- our Current Reports on Form 8-K filed with the SEC on [January 28, 2021](#), [March 8, 2021](#), [June 22, 2021](#), [July 19, 2021](#), [September 17, 2021](#) and [November 12, 2021](#) (solely with respect to Item 5.02);
- our Definitive Proxy Statement on [Schedule 14A](#), filed with the SEC on April 30, 2021 (but only with respect to information required by Part III of our Annual Report on Form 10-K for the year ended December 31, 2020, which information updated and superseded information included in Part III of our Annual Report on Form 10-K for the year ended December 31, 2020);
- the description of our common stock contained in our registration statement on [Form 8-A](#) filed with the SEC on September 16, 2020 under Section 12(b) of the Exchange Act, including any amendment or report filed for the purpose of updating such description, including [Exhibit 4.4](#) to our Annual Report on Form 10-K for the year ended December 31, 2020; and
- filings we make with the SEC pursuant to the Exchange Act after the date of the initial registration statement, of which this prospectus is a part, and prior to the effectiveness of the registration statement.

We will furnish without charge to you, on written or oral request, a copy of any or all of such documents that has been incorporated herein by reference (other than exhibits to such documents unless such exhibits are specifically incorporated by reference into the documents that this prospectus incorporates). Written or oral requests for copies should be directed to Prelude Therapeutics Incorporated, 200 Powder Mill Road, Wilmington, Delaware, 19803, and our telephone number is (302) 467-1280. See the section of this prospectus entitled “Where You Can Find More Information” for information concerning how to obtain copies of materials that we file with the SEC.

Any statement contained in this prospectus, or in a document, all or a portion of which is incorporated by reference, shall be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or any document incorporated by reference modifies or supersedes such statement. Any such statement so modified or superseded shall not, except as so modified or superseded, constitute a part of this prospectus.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds to us from the sale of our securities under this prospectus. Unless otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of securities under this prospectus for general corporate purposes, which may include funding research, clinical and process development and manufacturing of our product candidates, increasing our working capital, reducing indebtedness as applicable, acquisitions or investments in businesses, products or technologies that are complementary to our own and capital expenditures. We will set forth in the applicable prospectus supplement our intended use for the net proceeds received from the sale of any securities. We will not receive any of the proceeds from the sale of common stocks being offered by any of the selling stockholders.

SELLING STOCKHOLDERS

Pursuant to the Post-IPO Registration Rights Agreement, or Post-IPO RRA, between us and each of Baker Brothers and its affiliates, or Baker Bros., OrbiMed and its affiliates, or OrbiMed, and Kris Vaddi and his affiliated entities, the RRA Investors are entitled to rights, or the RRA-Investors' 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 amended and restated investors rights agreement by and among us and certain of our shareholders, or the investors rights agreement. 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. In accordance with this obligation, this prospectus also relates to the possible resale by Baker Bros or OrbiMed, who we refer to in this prospectus as the "selling stockholders," of up to 31,574,631 shares of our common stock held by such holders. Kris Vaddi and his affiliated entities have waived the RRA-Investors' rights in connection with the filing of this prospectus with respect to the shares held by them.

The following table sets forth the number of shares of common stock beneficially owned by the selling stockholders, the number of shares of common stock that may be offered under this prospectus and the number of shares of common stock beneficially owned by the selling stockholders assuming all of the shares covered hereby are sold. Percentage ownership of our common stock is based on 47,215,352 shares of our common stock outstanding on November 2, 2021 (of which 11,402,037 shares are non-voting common stock). We have determined beneficial ownership in accordance with the rules of the SEC, and thus it represents sole or shared voting or investment power with respect to our securities, and the information is not necessarily indicative of beneficial ownership for any other purpose. Unless otherwise indicated below, to our knowledge, the persons and entities named in the table have sole voting and sole investment power with respect to all shares that they beneficially owned, subject to community property laws where applicable. We have deemed all shares of common stock subject to options or other convertible securities held by that person or entity that are currently exercisable or that will become exercisable within 60 days of November 2, 2021 to be outstanding and to be beneficially owned by the person or entity holding the option for the purpose of computing the percentage ownership of that person or entity but have not treated them as outstanding for the purpose of computing the percentage ownership of any other person or entity. The number of shares of common stock in the column "Shares of common stock being offered by the selling stockholders" represents all of the common stock shares that the selling stockholders may offer hereunder. The selling stockholders may sell some, all or none of the common stock shares that may be offered hereunder. We do not know when the common stock shares will be sold by the selling stockholders, and the selling stockholders may offer the common stock shares from time to time.

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. The information under the heading "13(d) beneficial ownership" in the table below presents the beneficial ownership of the selling stockholders reflecting the 9.99% limitation. Solely for purposes of the table below, the information under the headings "Beneficial ownership before the offering" and "Beneficial ownership after the offering" disregards the 9.99% limitation. Unless otherwise indicated, the address of each beneficial owner listed in the table below is c/o Prelude Therapeutics Incorporated, 200 Powder Mill Road, Wilmington, Delaware 19803.

The information set forth below is based upon information obtained from the selling stockholders and upon information known to us.

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Julian Baker, a member of our board of directors, is affiliated with Baker Bros., and David Bonita, M.D., a member of our board of directors, is affiliated with OrbiMed.

	13(d) beneficial ownership(1)		Beneficial ownership before the offering(2)		Number of shares being offered by the selling stockholders	Beneficial ownership after the offering(2)(3)	
	Number of shares	%	Number of shares	%		Number of shares	%
Selling Stockholders							
Baker Bros. Advisors LP and Affiliates(4)	4,716,813	9.99	15,854,754	33.6	15,854,754	—	—
OrbiMed Entities(5)	4,716,813	9.99	15,719,877	33.3	15,719,877	—	—

(1) Reflects the 9.99% limitation on beneficial ownership described above.

(2) Solely for purposes of this table, disregards the 9.99% limitation on beneficial ownership described above.

(3) Assumes that all shares being registered in this prospectus are resold to third parties and that the selling stockholders sell all shares of common stock registered under this prospectus held by them or that they may acquire upon conversion of other classes of our common stock held by them.

(4) Based on information contained on a Schedule 13D/A filed January 29, 2021. Represents (i) 14,267 shares of voting common stock subject to options that are exercisable within 60 days of November 2, 2021 and 5,188 shares of voting common stock from exercise of options, (ii) 870,873 shares of our voting common stock and 509,480 shares of our non-voting common stock held by 667, L.P. (“667”) and (iii) 9,247,763 shares of our voting common stock and 5,212,371 shares of our non-voting common stock held by Baker Brothers Life Sciences, L.P. (“Life Sciences”, and together with 667 the “Baker Funds”). Baker Bros. Advisors LP, or the Adviser, serves as the investment adviser to the Baker Funds and has complete and unlimited discretion and authority with respect to their investments and voting power over the securities held by the Baker Funds. Baker Bros. Advisors (GP) LLC, or the Adviser GP, is the sole general partner of the Adviser. Julian C. Baker and Felix J. Baker are the managing members of the Adviser GP. The shares of non-voting common stock are only convertible to voting common stock to the extent that after giving effect to such conversion the holders thereof, together with their affiliates and any members of a Section 13(d) group with such holders, would beneficially own, for purposes of Rule 13d-3 under the Securities Exchange Act of 1934, as amended, no more than 9.99% of the outstanding shares of common stock (the “Beneficial Ownership Limitation”). By written notice to the Company, the Baker Funds may from time to time increase or decrease the Beneficial Ownership Limitation applicable to that Baker Fund to any other percentage not in excess of 19.99%. Any such change will not be effective until the 61st day after such notice is delivered to the Company. Julian C. Baker is also a member of our board of directors. Julian C. Baker, Felix J. Baker, the Adviser GP and the Adviser disclaim beneficial ownership of these securities held directly by the Baker Funds, except to the extent of their pecuniary interest therein. The address for the Adviser, the Adviser GP, Felix J. Baker and Julian C. Baker is c/o Baker Bros. Advisors LP, 860 Washington Street, 3rd Floor, New York, NY 10014.

(5) Based solely on information contained on a Schedule 13D/A filed January 14, 2021. Represents (i) 526,300 shares of voting common stock purchased by OrbiMed Partners Master Fund Limited, or OPM, (ii) 9,250,191 shares of voting common stock purchased by OrbiMed Private Investments VI, LP, or OPI VI, (iii) 263,200 shares of voting common stock purchased by The Biotech Growth Trust PLC, or BIOG, and together with OPM and OPI VI, the OrbiMed Entities, (iv) 5,596,886 shares of non-voting common stock purchased by OPI VI and (v) 83,300 shares of non-voting common stock purchased by BIOG. OrbiMed Capital GP VI LLC, or OrbiMed GP VI, is the general partner of OPI VI and OrbiMed Advisors LLC, or OrbiMed Advisors, a registered investment adviser under the Investment Advisors Act of 1940, as amended, is the managing member of OrbiMed GP VI. By virtue of such relationships, OrbiMed GP VI and OrbiMed

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Advisors may be deemed to have voting and investment power over the securities held by OPI VI and as a result may be deemed to have beneficial ownership over such securities. David Bonita, a member of OrbiMed Advisors, is a member of our board of directors. Each of OrbiMed GP VII, OrbiMed Advisors, and David Bonita disclaims beneficial ownership of the shares held by OPI VI, except to the extent of its or his pecuniary interest therein if any. OrbiMed Capital LLC, or OrbiMed Capital, is the portfolio manager to BIOG and the investment advisor to OPM. By virtue of such relationships, OrbiMed Capital may be deemed to have voting and investment power over the securities held by BIOG and OPM, and as a result may be deemed to have beneficial ownership over such securities. OrbiMed Capital is a relying advisor of OrbiMed Advisors. OrbiMed Capital and OrbiMed Advisors exercise voting and investment power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and W. Carter Neild. The address of the OrbiMed Entities is 601 Lexington Avenue, 54th Floor, New York, NY 10022.

PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus to one or more underwriters for public offering and sale by them, and may also sell the securities to investors directly or through agents. We will name any underwriter or agent involved in the offer and sale of securities in the applicable prospectus supplement. We have reserved the right to sell or exchange securities directly to investors on our own behalf in jurisdictions where we are authorized to do so. We may distribute the securities from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time. We will name in a prospectus supplement any agent involved in the offer or sale of our securities. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis, and a dealer will purchase securities as a principal for resale at varying prices to be determined by the dealer.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale and we will provide the name of any underwriter in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters or commissions from the purchasers for whom they may act as agent.

We will provide in the applicable prospectus supplement any compensation we pay to underwriters, dealers, or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act of 1933, as amended, or the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, and to reimburse them for certain expenses. We may grant underwriters who participate in the distribution of our securities under this prospectus an option to purchase additional securities to cover any over-allotments in connection with the distribution.

The securities we offer under this prospectus may or may not be listed through The Nasdaq Global Select Market or any other securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include short sales of the securities, which involves the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such short positions by making purchases in the open market or by exercising their option to purchase additional securities. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

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We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and they may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in these sale transactions will be an underwriter and will be identified in the applicable prospectus supplement. In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus. The financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

We will file a prospectus supplement to describe the terms of any offering of our securities covered by this prospectus. The prospectus supplement will disclose:

- the terms of the offer;
- the names of any underwriters, including any managing underwriters, as well as any dealers or agents;
- the purchase price of the securities from us;
- the net proceeds to us from the sale of the securities;
- any delayed delivery arrangements;
- any over-allotment or other options under which underwriters, if any, may purchase additional securities from us;
- any underwriting discounts, commissions or other items constituting underwriters' compensation, and any commissions paid to agents;
- in a subscription rights offering, whether we have engaged dealer-managers to facilitate the offering or subscription, including their name or names and compensation;
- any public offering price; and
- other facts material to the transaction.

We will bear all or substantially all of the costs, expenses and fees in connection with the registration of our securities under this prospectus. The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in two business days, unless the parties to any such trade expressly agree otherwise or the securities are sold by us to an underwriter in a firm commitment underwritten offering. The applicable prospectus supplement may provide that the original issue date for your securities may be more than two scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the second business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than two scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

Selling Stockholders Plan of Distribution

The selling stockholders may, from time to time, offer and sell up to 31,574,631 shares in the aggregate of our common stock, which we refer to as the Selling Stockholders Shares. The selling stockholders may, from time to time, sell, transfer or otherwise dispose of any or all of the Selling Stockholders Shares on any stock

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exchange, market or trading facility on which our common stock is traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices. To the extent any of the selling stockholders gift, pledge, grant a security interest in, distribute or otherwise transfer their Selling Stockholder Shares, such donees, pledgees, transferees or other successors-in-interest may offer and sell the shares from time to time under this prospectus, provided that this prospectus has been amended under applicable provision of the Securities Act to include the names of such donees, pledgees, transferees or other successors-in-interest as selling stockholders under this prospectus and such other information as may be necessary or required.

The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. They may use any one or more of the following methods when disposing of the Selling Stockholder Shares:

- ordinary brokerage transactions and transactions in which a broker-dealer solicits purchasers;
- block trades in which a broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- “at the market” or through market makers or into an existing market for the shares;
- short sales entered into after the effective date of the registration statement of which this prospectus is a part;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise, after the effective date of the registration statement of which this prospectus is a part;
- through the distribution of the shares by any selling stockholders to its partners, members or shareholders;
- through broker-dealers that agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- through one or more underwritten offerings on a firm commitment or best efforts basis;
- a combination of any such methods of sale; and
- any other method permitted pursuant to applicable law.

In connection with the sale of the Selling Stockholder Shares, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the shares in the course of hedging the positions they assume. The selling stockholders may also sell the Selling Stockholder Shares short and deliver these shares to close out their short positions, or loan or pledge the Selling Stockholder Shares to broker dealers that in turn may sell these shares. The selling stockholders may also enter into options or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of the Selling Stockholder Shares, which, subject to the amendment or supplement of this prospectus or the registration statement of which this prospectus forms a part to reflect such transaction and any other information necessary or required, such broker-dealer or other financial institution may resell pursuant to this registration statement.

The aggregate proceeds to the selling stockholders from the sale of the Selling Stockholder Shares will be the purchase price less discounts or commissions, if any. Each of the selling stockholders reserves the right to

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accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of its Selling Stockholder Shares to be made directly or through agents. We will not receive any of the proceeds from the sale of the Selling Stockholder Shares.

The selling stockholders also may resell all or a portion of the Selling Stockholder Shares in open market transactions in reliance upon Rule 144 under the Securities Act, provided that they meet the criteria and conform to the requirements of that rule.

The selling stockholders and any broker-dealers that act in connection with the sale of the Selling Stockholder Shares may be deemed to be “underwriters” within the meaning of Section 2(11) of the Securities Act in connection with such sales, and any commissions received by such broker-dealers and any profit on the resale of the securities sold by them while acting as principals may be deemed to be underwriting discounts or commissions under the Securities Act. In the event that any selling stockholder is deemed to be an “underwriter” within the meaning of Section 2(11) of the Securities Act, the selling stockholder will be subject to the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the Selling Stockholder Shares against certain liabilities, including liabilities arising under the Securities Act. To the extent required, the Selling Stockholder Shares to be sold, the names of the selling stockholders, the offering price, the names of any agents, dealers or underwriters, any commissions or discounts with respect to a particular offering, the method of distribution, and any other terms and conditions of the offering of such shares will be set forth in an accompanying prospectus supplement or, if appropriate, an amendment to the registration statement of which this prospectus forms a part.

To comply with the securities laws of some states, if applicable, the Selling Stockholder Shares may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the Selling Stockholder Shares may not be sold unless they have been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

The anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of the Selling Stockholder Shares in the market and to the activities of the selling stockholders and their affiliates. These rules may limit the timing of purchases and sales of the Selling Stockholder Shares by such selling stockholders. Regulation M may also restrict the ability of any person engaged in the distribution of the Selling Stockholder Shares to engage in market-making activities with respect to the shares. All of the foregoing may affect the marketability of the Selling Stockholder Shares and the ability of any person or entity to engage in market-making activities with respect to the Selling Stockholder Shares.

Pursuant to the Post-IPO RRA, we have agreed to bear all expenses in connection with the registration of the Selling Stockholder Shares. The selling stockholders have agreed to bear all underwriting discounts, selling commissions, and share transfer taxes applicable to the sale of the Selling Stockholder Shares, and fees and disbursements of counsel for the selling stockholders, other than the fees and disbursements of one counsel for the selling stockholders, which we have agreed to pay in an amount not to exceed \$50,000. We have also agreed to indemnify the selling stockholders against certain liabilities, including liabilities for violations of the Securities Act, Exchange Act and state securities laws and liabilities relating to this prospectus and the registration statement of which it forms a part, including amendments and supplements.

There can be no assurance that any selling stockholder will sell any or all of the Selling Stockholder Shares.

DESCRIPTION OF CAPITAL STOCK

The following description summarizes the most important terms of our capital stock, our restated certificate of incorporation and our restated bylaws. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description, you should refer to our restated certificate of incorporation and restated bylaws, which are included as exhibits to the registration statement of which this prospectus forms a part, and to the applicable provisions of Delaware law.

General

Our authorized capital stock consists of 487,149,741 shares of common stock, \$0.0001 par value per share, 12,850,259 shares of non-voting common stock, \$0.0001 par value per share, and 10,000,000 shares of undesignated preferred stock, \$0.0001 par value per share. Our board of directors is authorized, without stockholder approval, to issue additional shares of our capital stock.

Common Stock and Non-Voting Common Stock

Holders of our common stock have no conversion rights, while holders of our non-voting common stock have the right to convert each share of our non-voting common stock into one share of common stock at such holder's election, provided that as a result of such conversion, such holder, together with its affiliates and any members of a Schedule 13(d) group with such holder, would not beneficially own in excess of 9.99% of our common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in our restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder of non-voting common stock upon 61 days' notice to us.

Dividend Rights

Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of our common stock and our non-voting common stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine. See the section entitled "Dividend Policy."

Voting Rights

Except as otherwise expressly provided in our restated certificate of incorporation or as required by applicable law, on any matter that is submitted to a vote by our stockholders, holders of our common stock are entitled to one vote per share of common stock, and holders of our non-voting common stock are not entitled to any votes per share of non-voting common stock, including for the election of directors. We have not provided for cumulative voting for the election of directors in our restated certificate of incorporation, which means that holders of a majority of the shares of our common stock are able to elect all of our directors. Our restated certificate of incorporation established a classified board of directors, to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No Preemptive or Similar Rights

Neither our common stock nor our non-voting common stock is entitled to preemptive rights, and neither is subject to conversion, redemption or sinking fund provisions.

Right to Receive Liquidation Distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock and our non-voting common

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stock and any participating preferred stock outstanding at that time, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights of and the payment of liquidation preferences, if any, on any outstanding shares of preferred stock.

Preferred Stock

We had no shares of preferred stock outstanding as of September 30, 2021.

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders. Our board of directors is also able to increase or decrease the number of shares of any series of preferred stock, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock. We have no current plan to issue any shares of preferred stock.

Stock Options

As of September 30, 2021, we had outstanding options to purchase an aggregate 8,091,689 shares of our common stock, with a weighted average exercise price of \$15.30.

Registration Rights

As of September 30, 2021, the holders of 34,244,941 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 on March 23, 2021, if the holders of not less than 50% of the then-outstanding registrable securities may request the registration under the Securities Act of any registrable securities, if the anticipated aggregate offering price, net of selling expenses, would exceed \$10.0 million, we are obligated to provide notice of such request to all holders of registration rights and, as soon as practicable and in any event within 60 days, file a Form S-1 registration statement under the Securities Act covering all registrable securities that the initiating holders requested to be registered and any additional registrable securities requested to be included in such registration by any other holders. We are only required to file two registration statements that are declared effective upon exercise of these demand registration rights. We may postpone taking action with respect to such filing not more than once during any 12-month period for a period of not more than 90 days, if after receiving a request for registration, we furnish to the holders requesting such registration a certificate signed by our Chief Executive Officer stating that, in the good faith judgment of our board of directors, it would be materially detrimental to us and our stockholders; provided that we may not register any securities for our own account or that of any other stockholder during such 90-day period other than under certain circumstances.

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Form S-3 Registration Rights

The holders of at least 25% of the then-outstanding registrable securities can request that we register all or part of their shares on Form S-3 if we are eligible to file a registration statement on Form S-3 and if the aggregate price to the public of the shares offered, net of selling expenses, is at least \$5.0 million. The stockholders may only require us to effect two registration statements on Form S-3 in a 12-month period. We may postpone taking action with respect to such filing not more than once during any 12-month period for a period of not more than 90 days, if after receiving a request for registration, we furnish to the holders requesting such registration a certificate signed by our Chief Executive Officer stating that, in the good faith judgment of our board of directors, it would be materially detrimental to us and our stockholders; provided that we may not register any securities for our own account or that of any other stockholder during such 90-day period other than under certain circumstances.

Piggyback Registration Rights

If we register any of our securities for public sale in cash, holders of then-outstanding registrable securities or their permitted transferees will have the right to include their registrable securities in the registration statement. However, this right does not apply to a registration relating to any of our employee benefit plans, a corporate reorganization or transaction under Rule 145 of the Securities Act, a registration that requires information that is not substantially the same as the information required to be included in a registration statement covering the sale of the registrable securities, or a registration in which the only common stock being registered is common stock issuable upon conversion of debt securities that are also being registered or issuable upon the exercise of warrants. In an underwritten offering, if the total number of securities requested by stockholders to be included in the offering exceeds the number of securities to be sold (other than by us) that the underwriters determine in their reasonable discretion is compatible with the success of the offering, then we will be required to include only that number of securities that the underwriters and us, in our sole discretion, determine will not jeopardize the success of the offering. If the underwriters determine that less than all the registrable securities requested to be registered can be included in the offering, the number of registrable shares to be registered will be allocated (i) first, among holders of our preferred stock, in proportion to the amount of common stock issued or issuable upon conversion of the preferred stock owned by each such holder to be included in such offering, and (ii) second, among all other holders of our registrable securities, in proportion to the amount of other registrable securities owned by each such holder. However, (i) the number of shares issued or issuable upon conversion of the preferred stock, to be registered by the holders of our preferred stock, cannot be reduced unless all other securities (other than as offered by us) are first excluded entirely, and (ii) the number of shares to be registered by holders of all other registrable securities cannot be reduced unless all other securities (other than as offered by us and the shares of common stock issued or issuable on conversion of our preferred stock) are first entirely excluded. The number of registrable securities included in the offering may not be reduced below 25% of the total number of securities included in such offering, except for in connection with an initial public offering, in which case the underwriters may exclude these holders entirely.

Expenses of Registration Rights

We generally will pay all expenses, other than underwriting discounts and selling commissions incurred in connection with each of the registrations described above, including the reasonable fees and disbursements, not to exceed \$15,000, of one counsel for the selling holders.

Expiration of Registration Rights

The registration rights described above will expire, with respect to any particular holder of these rights, on the earliest to occur of (a) at such time that all of the holder's registrable securities can be sold without limitation in any three-month period without registration in compliance with Rule 144 or a similar exemption under the Securities Act and (b) at such time that our common stock is trading on a national securities exchange and all of the holder's registrable securities can be sold during a three-month period without registration.

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Registration Rights Agreement

Pursuant to the Post-IPO RRA between us and each of Baker Brothers and its affiliates, OrbiMed and its affiliates and Kris Vaddi and his affiliated entities, the RRA Investors are entitled to rights with respect to the registration of their shares under the Securities Act that supersede such rights as described above held by the RRA Investors under the IRA. These registration rights include the right to demand that we file with the SEC a Form S-3 registration statement (except if we are not then eligible to register for resale the registrable securities on Form S-3, in which case, such registration shall be on another appropriate form in accordance with the Securities Act) covering the registration of their registrable securities for resale, subject to certain conditions, as well as rights to be permitted an aggregate of five underwritten public offerings between the RRA Investors during the term of the Post-IPO RRA, subject to a limitation of an aggregate of two underwritten public offerings per calendar year, to effect the sale of their common stock for sale. The RRA Investors also have piggy-back rights to participate in registrations demanded by any of the other RRA Investors. The Post-IPO RRA requires us to pay expenses relating to such registrations and indemnify these holders against certain liabilities. Our registration obligations under this registration rights agreement would continue in effect until the earliest of (i) December 20, 2030, (ii) when the applicable registrable securities have been resold by the holders pursuant to an effective registration statement, (iii) when the applicable registrable securities have been resold pursuant to Rule 144 or (iv) when the applicable registrable securities may be resold pursuant to Rule 144 without limitations as to volume or manner of sale.

Anti-Takeover Provisions

The provisions of Delaware General Corporation Law, or DGCL, our restated certificate of incorporation and our restated bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of our company. These provisions, which are summarized below, may have the effect of discouraging takeover bids. They are also designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging a proposal to acquire us because negotiation of these proposals could result in an improvement of their terms.

Delaware Law

We are subject to the provisions of Section 203 of the DGCL regulating corporate takeovers. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a “business combination” with an “interested stockholder” for a period of three years following the date on which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, (i) shares owned by persons who are directors and also officers and (ii) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66.67% of the outstanding voting stock that is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction or series of transactions together resulting in a financial benefit to the interested stockholder. An interested stockholder is a

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person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. We expect the existence of this provision to have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. We also anticipate that Section 203 may also discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

Anti-Takeover Effects of Certain Provisions of Our Restated Certificate of Incorporation and Restated Bylaw

Our restated certificate of incorporation and our restated bylaws include a number of provisions that could deter hostile takeovers or delay or prevent changes in control of our company, including the following:

- *Board of Directors Vacancies.* Our restated certificate of incorporation and restated bylaws authorizes only our board of directors to fill vacant directorships, including newly created seats. In addition, the number of directors constituting our board of directors is permitted to be set only by a resolution adopted by a majority vote of our entire board of directors. These provisions would prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.
- *Classified Board.* Our restated certificate of incorporation and restated bylaws provide that our board of directors is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors. See the section entitled "Management—Board Composition."
- *Stockholder Action; Special Meetings of Stockholders.* Our restated certificate of incorporation provide that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock would not be able to amend our restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our restated bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, our Chief Executive Officer or our President, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.
- *Advance Notice Requirements for Stockholder Proposals and Director Nominations.* Our restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our restated bylaws also specify certain requirements regarding the form and content of a stockholder's notice. These provisions might preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions might also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.
- *No Cumulative Voting.* The DGCL provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our restated certificate of incorporation and restated bylaws do not provide for cumulative voting.
- *Directors Removed Only for Cause.* Our restated certificate of incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of the holders of at least two-thirds of our outstanding common stock.

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- *Amendment of Charter Provisions.* Any amendment of the above provisions in our restated certificate of incorporation would require approval by holders of at least two-thirds of our outstanding common stock.
- *Issuance of Undesignated Preferred Stock.* Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock would enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by merger, tender offer, proxy contest or other means.
- *Choice of Forum.* Our restated certificate of incorporation provides that, to the fullest extent permitted by law, the Court of Chancery of the State of Delaware will be the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our restated certificate of incorporation or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable. Our restated bylaws also provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court which recently found that such provisions are facially valid under Delaware law or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court. Neither the exclusive forum provision nor the Federal Forum Provision applies to suits brought to enforce any duty or liability created by the Exchange Act. Section 27 of the Exchange Act creates exclusive federal jurisdiction over all claims brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. Accordingly, actions by our stockholders to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder also must be brought in federal court. Our stockholders will not be deemed to have waived our compliance with the federal securities laws and the regulations promulgated thereunder. Any person or entity purchasing or otherwise acquiring or holding any interest in any of our securities shall be deemed to have notice of and consented to our exclusive forum provisions, including the Federal Forum Provision. These provisions may limit a stockholder's ability to bring a claim in a judicial forum of their choosing for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock and non-voting common stock is Computershare Trust Company, N.A.

The Nasdaq Global Select Market Listing

Our common stock is listed on The Nasdaq Global Select Market under the symbol "PRLD." The non-voting common stock 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.

DESCRIPTION OF DEBT SECURITIES

General

We will issue the debt securities offered by this prospectus and any accompanying prospectus supplement under an indenture to be entered into between us and the trustee identified in the applicable prospectus supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have filed a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

We may offer under this prospectus up to an aggregate principal amount of \$400,000,000 in debt securities, or if debt securities are issued at a discount, or in a foreign currency, foreign currency units or composite currency, the principal amount as may be sold for an aggregate public offering price of up to \$400,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent our direct, unsecured obligations and will rank equally with all of our other unsecured indebtedness.

We may issue the debt securities in one or more series with the same or various maturities, at par, at a premium, or at a discount. We will describe the particular terms of each series of debt securities in a prospectus supplement relating to that series, which we will file with the SEC. The prospectus supplement relating to the particular series of debt securities being offered will specify the particular amounts, prices and terms of those debt securities. These terms may include:

- the title of the series;
- the aggregate principal amount, and, if a series, the total amount authorized and the total amount outstanding;
- the issue price or prices, expressed as a percentage of the aggregate principal amount of the debt securities;
- any limit on the aggregate principal amount;
- the date or dates on which principal is payable;
- the interest rate or rates (which may be fixed or variable) or, if applicable, the method used to determine such rate or rates;
- the date or dates from which interest, if any, will be payable and any regular record date for the interest payable;
- the place or places where principal and, if applicable, premium and interest, is payable;
- the terms and conditions upon which we may, or the holders may require us to, redeem or repurchase the debt securities;
- the denominations in which such debt securities may be issuable, if other than denominations of \$1,000 or any integral multiple of that number;
- whether the debt securities are to be issuable in the form of certificated securities (as described below) or global securities (as described below);
- the portion of principal amount that will be payable upon declaration of acceleration of the maturity date if other than the principal amount of the debt securities;
- the currency of denomination;
- the designation of the currency, currencies or currency units in which payment of principal and, if applicable, premium and interest, will be made;

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- if payments of principal and, if applicable, premium or interest, on the debt securities are to be made in one or more currencies or currency units other than the currency of denomination, the manner in which the exchange rate with respect to such payments will be determined;
- if amounts of principal and, if applicable, premium and interest may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index, then the manner in which such amounts will be determined;
- the provisions, if any, relating to any collateral provided for such debt securities;
- any addition to or change in the covenants and/or the acceleration provisions described in this prospectus or in the indenture;
- any events of default, if not otherwise described below under “Events of Default”;
- the terms and conditions, if any, for conversion into or exchange for shares of our common stock or preferred stock;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents; and
- the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to our other indebtedness.

We may issue discount debt securities that provide for an amount less than the stated principal amount to be due and payable upon acceleration of the maturity of such debt securities in accordance with the terms of the indenture. We may also issue debt securities in bearer form, with or without coupons. If we issue discount debt securities or debt securities in bearer form, we will describe material U.S. federal income tax considerations and other material special considerations which apply to these debt securities in the applicable prospectus supplement.

We may issue debt securities denominated in or payable in a foreign currency or currencies or a foreign currency unit or units. If we do, we will describe the restrictions, elections, and general tax considerations relating to the debt securities and the foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Debt securities offered under this prospectus and any prospectus supplement will be subordinated in right of payment to certain of our outstanding senior indebtedness. In addition, we will seek the consent of the holders of any such senior indebtedness prior to issuing any debt securities under this prospectus to the extent required by the agreements evidencing such senior indebtedness.

Registrar and Paying Agent

The debt securities may be presented for registration of transfer or for exchange at the corporate trust office of the security registrar or at any other office or agency that we maintain for those purposes. In addition, the debt securities may be presented for payment of principal, interest and any premium at the office of the paying agent or at any office or agency that we maintain for those purposes.

Conversion or Exchange Rights

Debt securities may be convertible into or exchangeable for shares of our common stock. The terms and conditions of conversion or exchange will be stated in the applicable prospectus supplement. The terms will include, among others, the following:

- the conversion or exchange price;
- the conversion or exchange period;

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- provisions regarding the convertibility or exchangeability of the debt securities, including who may convert or exchange;
- events requiring adjustment to the conversion or exchange price;
- provisions affecting conversion or exchange in the event of our redemption of the debt securities; and
- any anti-dilution provisions, if applicable.

Registered Global Securities

If we decide to issue debt securities in the form of one or more global securities, then we will register the global securities in the name of the depositary for the global securities or the nominee of the depositary, and the global securities will be delivered by the trustee to the depositary for credit to the accounts of the holders of beneficial interests in the debt securities.

The prospectus supplement will describe the specific terms of the depositary arrangement for debt securities of a series that are issued in global form. None of us, the trustee, any payment agent or the security registrar will have any responsibility or liability for any aspect of the records relating to or payments made on account of beneficial ownership interests in a global debt security or for maintaining, supervising or reviewing any records relating to these beneficial ownership interests.

No Protection in the Event of Change of Control

The indenture does not have any covenants or other provisions providing for a put or increased interest or otherwise that would afford holders of our debt securities additional protection in the event of a recapitalization transaction, a change of control or a highly leveraged transaction. If we offer any covenants or provisions of this type with respect to any debt securities covered by this prospectus, we will describe them in the applicable prospectus supplement.

Covenants

Unless otherwise indicated in this prospectus or the applicable prospectus supplement, our debt securities will not have the benefit of any covenants that limit or restrict our business or operations, the pledging of our assets or the incurrence by us of indebtedness. We will describe in the applicable prospectus supplement any material covenants in respect of a series of debt securities.

Merger, Consolidation or Sale of Assets

The form of indenture provides that we will not consolidate with or merge into any other person or convey, transfer, sell or lease our properties and assets substantially as an entirety to any person, unless:

- we are the surviving person of such merger or consolidation, or if we are not the surviving person, the person formed by the consolidation or into or with which we are merged or the person to which our properties and assets are conveyed, transferred, sold or leased, is a corporation organized and existing under the laws of the U.S., any state or the District of Columbia or a corporation or comparable legal entity organized under the laws of a foreign jurisdiction and has expressly assumed all of our obligations, including the payment of the principal of and, premium, if any, and interest on the debt securities and the performance of the other covenants under the indenture; and
- immediately before and immediately after giving effect to the transaction on a pro forma basis, no event of default, and no event which, after notice or lapse of time or both, would become an event of default, has occurred and is continuing under the indenture.

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Events of Default

Unless otherwise specified in the applicable prospectus supplement, the following events will be events of default under the indenture with respect to debt securities of any series:

- we fail to pay any principal or premium, if any, when it becomes due;
- we fail to pay any interest within 30 days after it becomes due;
- we fail to observe or perform any other covenant in the debt securities or the indenture for 90 days after written notice specifying the failure from the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of that series; and certain events involving bankruptcy, insolvency or reorganization of us or any of our significant subsidiaries.

The trustee may withhold notice to the holders of the debt securities of any series of any default, except in payment of principal of or premium, if any, or interest on the debt securities of a series, if the trustee considers it to be in the best interest of the holders of the debt securities of that series to do so.

If an event of default (other than an event of default resulting from certain events of bankruptcy, insolvency or reorganization) occurs, and is continuing, then the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of any series may accelerate the maturity of the debt securities. If this happens, the entire principal amount, plus the premium, if any, of all the outstanding debt securities of the affected series plus accrued interest to the date of acceleration will be immediately due and payable. At any time after the acceleration, but before a judgment or decree based on such acceleration is obtained by the trustee, the holders of a majority in aggregate principal amount of outstanding debt securities of such series may rescind and annul such acceleration if:

- all events of default (other than nonpayment of accelerated principal, premium or interest) have been cured or waived;
- all lawful interest on overdue interest and overdue principal has been paid; and
- the rescission would not conflict with any judgment or decree.

In addition, if the acceleration occurs at any time when we have outstanding indebtedness that is senior to the debt securities, the payment of the principal amount of outstanding debt securities may be subordinated in right of payment to the prior payment of any amounts due under the senior indebtedness, in which case the holders of debt securities will be entitled to payment under the terms prescribed in the instruments evidencing the senior indebtedness and the indenture.

If an event of default resulting from certain events of bankruptcy, insolvency or reorganization occurs, the principal, premium and interest amount with respect to all of the debt securities of any series will be due and payable immediately without any declaration or other act on the part of the trustee or the holders of the debt securities of that series.

The holders of a majority in principal amount of the outstanding debt securities of a series will have the right to waive any existing default or compliance with any provision of the indenture or the debt securities of that series and to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, subject to certain limitations specified in the indenture.

No holder of any debt security of a series will have any right to institute any proceeding with respect to the indenture or for any remedy under the indenture, unless:

- the holder gives to the trustee written notice of a continuing event of default;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of the affected series make a written request and offer reasonable indemnity to the trustee to institute a proceeding as trustee;

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- the trustee fails to institute a proceeding within 60 days after such request; and
- the holders of a majority in aggregate principal amount of the outstanding debt securities of the affected series do not give the trustee a direction inconsistent with such request during such 60-day period.

These limitations do not, however, apply to a suit instituted for payment on debt securities of any series on or after the due dates expressed in the debt securities.

We will periodically deliver certificates to the trustee regarding our compliance with our obligations under the indenture.

Modification and Waiver

From time to time, we and the trustee may, without the consent of holders of the debt securities of one or more series, amend the indenture or the debt securities of one or more series, or supplement the indenture, for certain specified purposes, including:

- to provide that the surviving entity following a change of control permitted under the indenture will assume all of our obligations under the indenture and debt securities;
- to provide for certificated debt securities in addition to uncertificated debt securities;
- to comply with any requirements of the SEC under the Trust Indenture Act of 1939;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;
- to cure any ambiguity, defect or inconsistency, or make any other change that does not materially and adversely affect the rights of any holder; and
- to appoint a successor trustee under the indenture with respect to one or more series.

From time to time we and the trustee may, with the consent of holders of at least a majority in principal amount of an outstanding series of debt securities, amend or supplement the indenture or the debt securities series, or waive compliance in a particular instance by us with any provision of the indenture or the debt securities. We may not, however, without the consent of each holder affected by such action, modify or supplement the indenture or the debt securities or waive compliance with any provision of the indenture or the debt securities in order to:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement, or waiver to the indenture or such debt security;
- reduce the rate of or change the time for payment of interest or reduce the amount of or postpone the date for payment of sinking fund or analogous obligations;
- reduce the principal of or change the stated maturity of the debt securities;
- make any debt security payable in money other than that stated in the debt security;
- change the amount or time of any payment required or reduce the premium payable upon any redemption, or change the time before which no such redemption may be made;
- waive a default in the payment of the principal of, premium, if any, or interest on the debt securities or a redemption payment;
- waive a redemption payment with respect to any debt securities or change any provision with respect to redemption of debt securities; or

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- take any other action otherwise prohibited by the indenture to be taken without the consent of each holder affected by the action.

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

The indenture permits us, at any time, to elect to discharge our obligations with respect to one or more series of debt securities by following certain procedures described in the indenture. These procedures will allow us either:

- to defease and be discharged from any and all of our obligations with respect to any debt securities except for the following obligations (which discharge is referred to as “legal defeasance”):
 1. to register the transfer or exchange of such debt securities;
 2. to replace temporary or mutilated, destroyed, lost or stolen debt securities;
 3. to compensate and indemnify the trustee; or
 4. to maintain an office or agency in respect of the debt securities and to hold monies for payment in trust; or
 5. to be released from our obligations with respect to the debt securities under certain covenants contained in the indenture, as well as any additional covenants which may be contained in the applicable supplemental indenture (which release is referred to as “covenant defeasance”).

In order to exercise either defeasance option, we must irrevocably deposit with the trustee or other qualifying trustee, in trust for that purpose:

- money;
- U.S. Government Obligations (as described below) or Foreign Government Obligations (as described below) that through the scheduled payment of principal and interest in accordance with their terms will provide money; or
- a combination of money and/or U.S. Government Obligations and/or Foreign Government Obligations sufficient in the written opinion of a nationally-recognized firm of independent accountants to provide money;

that, in each case specified above, provides a sufficient amount to pay the principal of, premium, if any, and interest, if any, on the debt securities of the series, on the scheduled due dates or on a selected date of redemption in accordance with the terms of the indenture.

In addition, defeasance may be effected only if, among other things:

- in the case of either legal or covenant defeasance, we deliver to the trustee an opinion of counsel, as specified in the indenture, stating that as a result of the defeasance neither the trust nor the trustee will be required to register as an investment company under the Investment Company Act of 1940;
- in the case of legal defeasance, we deliver to the trustee an opinion of counsel stating that we have received from, or there has been published by, the Internal Revenue Service a ruling to the effect that, or there has been a change in any applicable federal income tax law with the effect that (and the opinion shall confirm that), the holders of outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes solely as a result of such legal defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner, including as a result of prepayment, and at the same times as would have been the case if legal defeasance had not occurred;
- in the case of covenant defeasance, we deliver to the trustee an opinion of counsel to the effect that the holders of the outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes as a result of covenant defeasance and will be subject to U.S. federal income tax

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- on the same amounts, in the same manner and at the same times as would have been the case if covenant defeasance had not occurred; and
- certain other conditions described in the indenture are satisfied.

If we fail to comply with our remaining obligations under the indenture and applicable supplemental indenture after a covenant defeasance of the indenture and applicable supplemental indenture, and the debt securities are declared due and payable because of the occurrence of any undefeased event of default, the amount of money and/or U.S. Government Obligations and/or Foreign Government Obligations on deposit with the trustee could be insufficient to pay amounts due under the debt securities of the affected series at the time of acceleration. We will, however, remain liable in respect of these payments.

The term “U.S. Government Obligations” as used in the above discussion means securities that are direct obligations of or non-callable obligations guaranteed by the United States of America for the payment of which obligation or guarantee the full faith and credit of the United States of America is pledged.

The term “Foreign Government Obligations” as used in the above discussion means, with respect to debt securities of any series that are denominated in a currency other than U.S. dollars, (1) direct obligations of the government that issued or caused to be issued such currency for the payment of which obligations its full faith and credit is pledged or (2) obligations of a person controlled or supervised by or acting as an agent or instrumentality of such government the timely payment of which is unconditionally guaranteed as a full faith and credit obligation by that government, which in either case under clauses (1) or (2), are not callable or redeemable at the option of the issuer.

Regarding the Trustee

We will identify the trustee with respect to any series of debt securities in the prospectus supplement relating to the applicable debt securities. You should note that if the trustee becomes a creditor of ours, the indenture and the Trust Indenture Act of 1939 limit the rights of the trustee to obtain payment of claims in certain cases, or to realize on certain property received in respect of any such claim, as security or otherwise. The trustee and its affiliates may engage in, and will be permitted to continue to engage in, other transactions with us and our affiliates. If, however, the trustee acquires any “conflicting interest” within the meaning of the Trust Indenture Act of 1939, it must eliminate such conflict or resign.

The holders of a majority in principal amount of the then outstanding debt securities of any series may direct the time, method and place of conducting any proceeding for exercising any remedy available to the trustee. If an event of default occurs and is continuing, the trustee, in the exercise of its rights and powers, must use the degree of care and skill of a prudent person in the conduct of his or her own affairs. Subject to that provision, the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any of the holders of the debt securities, unless they have offered to the trustee reasonable indemnity or security.

No Individual Liability of Incorporators, Stockholders, Officers or Directors

Each indenture provides that no incorporator and no past, present or future stockholder, officer or director of our company or any successor corporation in those capacities will have any individual liability for any of our obligations, covenants or agreements under the debt securities or such indenture.

Governing Law

The indentures and the debt securities will be governed by, and construed in accordance with, the laws of the State of New York.

DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of our debt securities, preferred stock, common stock, or any combination thereof. Warrants may be issued independently or together with our debt securities, preferred stock or common stock and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a bank or trust company, as warrant agent. The warrant agent will act solely as our agent in connection with the warrants. The warrant agent will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants. This summary of certain provisions of the warrants is not complete. For the terms of a particular series of warrants, you should refer to the prospectus supplement for that series of warrants and the warrant agreement for that particular series.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to purchase debt securities will describe the terms of the debt warrants, including the following:

- the title of the debt warrants;
- the offering price for the debt warrants, if any;
- the aggregate number of the debt warrants;
- the designation and terms of the debt securities, including any conversion rights, purchasable upon exercise of the debt warrants;
- if applicable, the date from and after which the debt warrants and any debt securities issued with them will be separately transferable;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the dates on which the right to exercise the debt warrants will commence and expire;
- if applicable, the minimum or maximum amount of the debt warrants that may be exercised at any one time;
- whether the debt warrants represented by the debt warrant certificates or debt securities that may be issued upon exercise of the debt warrants will be issued in registered or bearer form;
- information with respect to book-entry procedures, if any;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material U.S. federal income tax considerations;
- the antidilution provisions of the debt warrants, if any;
- the redemption or call provisions, if any, applicable to the debt warrants;
- any provisions with respect to the holder's right to require us to repurchase the debt warrants upon a change in control or similar event; and
- any additional terms of the debt warrants, including procedures and limitations relating to the exchange, exercise, and settlement of the debt warrants.

Debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations. Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in

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the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or any premium, if any, or interest on the debt securities purchasable upon exercise.

Equity Warrants

The prospectus supplement relating to a particular series of warrants to purchase our common stock or preferred stock will describe the terms of the warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of warrants;
- the designation and terms of the common stock or preferred stock that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or preferred stock that may be purchased upon exercise of a warrant and the exercise price for the warrants;
- the dates on which the right to exercise the warrants shall commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material U.S. federal income tax considerations;
- the antidilution provisions of the warrants, if any;
- the redemption or call provisions, if any, applicable to the warrants;
- any provisions with respect to a holder's right to require us to repurchase the warrants upon a change in control or similar event; and
- any additional terms of the warrants, including procedures and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent, or receive dividends;
- receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- exercise any rights as stockholders.

DESCRIPTION OF SUBSCRIPTION RIGHTS

We may issue subscription rights to purchase our common stock, preferred stock or debt securities. These subscription rights may be offered independently or together with any other security offered hereby and may or may not be transferable by the stockholder receiving the subscription rights in such offering. In connection with any offering of subscription rights, we may enter into a standby arrangement with one or more underwriters or other purchasers pursuant to which the underwriters or other purchasers may be required to purchase any securities remaining unsubscribed for after such offering.

The prospectus supplement relating to any subscription rights we offer, if any, will, to the extent applicable, include specific terms relating to the offering, including some or all of the following:

- the price, if any, for the subscription rights;
- the exercise price payable for our common stock, preferred stock or debt securities upon the exercise of the subscription rights;
- the number of subscription rights to be issued to each stockholder;
- the number and terms of our common stock, preferred stock or debt securities which may be purchased per each subscription right;
- the extent to which the subscription rights are transferable;
- any other terms of the subscription rights, including the terms, procedures and limitations relating to the exchange and exercise of the subscription rights;
- the date on which the right to exercise the subscription rights shall commence, and the date on which the subscription rights shall expire;
- the extent to which the subscription rights may include an over-subscription privilege with respect to unsubscribed securities or an over-allotment privilege to the extent the securities are fully subscribed; and
- if applicable, the material terms of any standby underwriting or purchase arrangement which may be entered into by us in connection with the offering of subscription rights.

The description in the applicable prospectus supplement of any subscription rights we offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable subscription rights certificate, which will be filed with the SEC if we offer subscription rights. We urge you to read the applicable subscription rights certificate and any applicable prospectus supplement in their entirety.

DESCRIPTION OF UNITS

We may issue units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the applicable prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

LEGAL MATTERS

Fenwick & West LLP, San Francisco, California, will issue an opinion about certain legal matters with respect to the securities. Any underwriters, selling stockholders or agents will be advised about legal matters relating to any offering by their own counsel.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our [Annual Report on Form 10-K for the year ended December 31, 2020](#), as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.



4,496,744 Shares of Common Stock
Pre-Funded Warrants to Purchase 12,895,256 Shares of Common Stock

PROSPECTUS SUPPLEMENT

Morgan Stanley

May 18, 2023