

PROSPECTUS SUPPLEMENT
(to Prospectus dated November 24, 2021)



Up to \$75,000,000
Common Stock

We have entered into an Open Market Sale AgreementSM, or Sales Agreement, with Jefferies LLC, or Jefferies, relating to shares of our common stock, par value \$0.0001 per share, offered by this prospectus supplement. In accordance with the terms of the Sales Agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$75.0 million from time to time through Jefferies acting as our agent.

Our common stock is traded on The Nasdaq Global Select Market under the symbol “PRLD.” The last reported sales price of our common stock on The Nasdaq Global Select Market on March 14, 2023, was \$6.01 per share.

Sales of our common stock, if any, under this prospectus supplement may be made in sales deemed to be an “at the market offering” as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended, or the Securities Act. Jefferies is not required to sell any specific number or dollar amount of securities, but will act as a sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, on mutually agreed terms between Jefferies and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to Jefferies for sales of common stock sold pursuant to the Sales Agreement will be up to 3.0% of the aggregate gross proceeds of any shares of common stock sold under the Sales Agreement. In connection with the sale of the common stock on our behalf, Jefferies will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Jefferies will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Jefferies with respect to certain liabilities, including liabilities under the Securities Act or the Securities Exchange Act of 1934, as amended, or the Exchange Act. See “Plan of Distribution” beginning on page S-15 regarding the compensation to be paid to Jefferies.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties referenced under the heading “[Risk Factors](#)” on page S-9 of this prospectus supplement as well as those contained in the accompanying prospectus and any related free writing prospectus or prospectus supplement we prepare or authorize in connection with this offering, and in the other documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus.

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.

Jefferies

The date of this prospectus supplement is March 15, 2023.

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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. Under this prospectus supplement and the accompanying prospectus, we may from time to time sell shares of our common stock having an aggregate offering price of up to \$75.0 million, at prices and on terms to be determined by market conditions at the time of the offering.

This document is in two parts. The first part is a prospectus supplement, which describes the specific terms of this offering and certain other matters relating to us. The second part is the accompanying prospectus, which provides more general information, some of which may not apply to this offering. You should read both this prospectus supplement and the accompanying prospectus as well as the additional information described in this prospectus supplement under the headings “Where You Can Find More Information” and “Incorporation of Information by Reference” before investing in our common stock.

This prospectus supplement describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. To the extent that any statement that we make in this prospectus supplement is inconsistent with the statements made in the accompanying prospectus or in any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, the statements made in the accompanying prospectus, or such earlier filing, as applicable, are deemed modified or superseded by the statements made in this prospectus supplement. 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 supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

You should rely only on the information contained or incorporated by reference in this prospectus supplement. We have not, and Jefferies has not, authorized anyone to provide you with any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or any accompanying prospectus supplement or related free writing prospectus to which we have referred you. Neither we nor Jefferies take any responsibility for, and can provide no assurance as to the reliability of, any other information others may give you. We are not, and Jefferies is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein and any prospectus supplement or free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus supplement were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein and any prospectus supplement or free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where such offers and sales are permitted. The distribution of this prospectus supplement and the offering of our common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into

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possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of our common stock 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.

WHERE YOU CAN FIND MORE INFORMATION

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.

Copies of our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, proxy statements and amendments, if any, to those reports filed or furnished with the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act and additional 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 or the accompanying prospectus and is not incorporated by reference into this prospectus supplement or the accompanying prospectus.

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 that we filed with the SEC under the Securities Act. This prospectus supplement and the accompany prospectus do 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. The full registration statement may be obtained from the SEC or us, as provided below. Statements contained in this prospectus supplement or the accompanying 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. You may inspect a copy of the registration statement through the SEC's website, as provided above.

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

We will provide to each person, including any beneficial owner, to whom a prospectus supplement is delivered, without charge, upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus supplement but not delivered with this prospectus supplement, excluding any exhibits to those documents unless the exhibit is specifically incorporated by reference as an exhibit in this prospectus supplement. You should direct requests for documents to:

Prelude Therapeutics Incorporated
Attn: Chief Legal Officer
200 Powder Mill Road
Wilmington, Delaware 19803
(302) 467-1280

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 information we file later with the SEC will automatically update and supersede this information. 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 supplement and the accompanying prospectus (other than information in such filings that was “furnished,” under applicable SEC rules, rather than “filed”):

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2022, filed with the SEC on March 15, 2023;
- our Current Report on [Form 8-K](#) filed with the SEC on January 23, 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, 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, 2022.

We will furnish without charge to you, on written or oral request, a copy of any or all of such documents that have 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 supplement or the accompanying prospectus 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 titled “Where You Can Find More Information” for information concerning how to obtain copies of materials that we file with the SEC.

To the extent that any statement that we make in this prospectus supplement is inconsistent with the statements made in the accompanying prospectus or in any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, the statements made in the accompanying prospectus, or such earlier filing, as applicable, are deemed modified or superseded by the statements made in this prospectus supplement. 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 supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

SUMMARY

This summary highlights information contained elsewhere in this prospectus supplement. Before investing in our common stock, you should carefully read this entire prospectus, including our consolidated financial statements and the related footnotes and the other documents incorporated by reference herein.

Company Overview

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, or the FDA, 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.

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 cyclin-dependent kinase 9, or 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 intravenous, or IV, doses of PRT2527 as a monotherapy in patients with selected solid tumors. No adverse events leading to dose reduction or discontinuation have been reported, and we expect to select a Recommended Phase 2 Dose, or RP2D, in solid tumors. We plan to use this safety data to continue the cohort expansion study in solid tumors, as well as to inform and rapidly progress PRT2527 in a hematology malignancies clinical trial. We expect to present solid tumor dose escalation data at a medical conference in the first half of 2023, demonstrate a RP2D in hematological malignancies in the second half of 2023, and present initial clinical results for hematological malignancies at a medical conference 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. In this study, PRT1419 has been generally well tolerated, with no cardiotoxicity observed in these patients to date. Cardiovascular parameters including troponin levels and ejection fraction changes were evaluated, in addition to standard safety, pharmacokinetics and target engagement metrics. 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. We intend to evaluate PRT1419 in hematology malignancies in monotherapy, as well as in combinations, with the goal of establishing safety, clinical activity and a RP2D in hematology malignancies in 2023. Advancement in hematological cancers will include monotherapy expansions in chronic lymphocytic leukemia, or CLL, and non-Hodgkin's lymphoma, or NHL, based on a strong rationale for MCL1 inhibition and the need for novel treatments in second line. We expect to present solid tumor data at a medical conference in the first half of 2023, demonstrate a RP2D in hematological malignancies in the second half of 2023, and present hematological malignancy data in the second half of 2023.

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, and our first patient was dosed in December 2022.

In October 2022, we received IND clearance for PRT3879, 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.

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.

Company 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. 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, or the Sarbanes-Oxley Act;

- 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 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	Shares of our common stock having an aggregate offering price of up to \$75.0 million.
Common stock to be outstanding immediately after this offering	Up to 60,610,895 shares (as more fully described in the notes following this table), assuming sales of 12,711,864 shares of our common stock in this offering at an offering price of \$5.90 per share, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on March 13, 2023. The actual number of shares issued will vary depending on the sales price under this offering.
Plan of Distribution	“At the market offering” that may be made from time to time through our sales agent, Jefferies LLC. See “Plan of Distribution.”
Use of Proceeds	We currently intend to use the net proceeds of this offering primarily for general corporate purposes, which may include funding research, preclinical and clinical development of our product candidates, increasing our working capital and capital expenditures. See “Use of Proceeds.”
Risk Factors	Investing in our common stock involves significant risks. See the disclosure under the heading “Risk Factors” in this prospectus supplement and the accompanying prospectus and under similar headings in our Annual Report on Form 10-K for the year ended December 31, 2022 and other documents incorporated by reference into this prospectus supplement and the accompanying prospectus.
The Nasdaq Global Select Market symbol	“PRLD”

The number of shares of our common stock and non-voting common stock to be outstanding after this offering is based on 47,899,031 shares of common stock and non-voting common stock (of which 11,402,037 shares are non-voting common stock) outstanding as of December 31, 2022 (including 201,716 unvested restricted shares outstanding as of December 31, 2022) and excludes:

- 9,390,930 shares of common stock issuable upon the exercise of stock options outstanding as of December 31, 2022 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 \$12.08 per share;
- 2,680,178 shares of common stock issuable upon the exercise of stock options granted after December 31, 2022 under the 2020 Plan with an exercise price of \$7.02; and
- 6,449,187 shares of common stock reserved for future issuance as of December 31, 2022 under our stock-based compensation plans, consisting of (i) 5,139,028 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 1,310,159 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan.

RISK FACTORS

Investment in any securities offered pursuant to this prospectus supplement and the accompanying prospectus involves risks. You should carefully consider the risk factors described below, in our Annual Report on Form 10-K for the fiscal year ended December 31, 2022, incorporated by reference in this prospectus supplement, any amendment or update thereto reflected in subsequent filings with the SEC, including in our Quarterly Reports on Form 10-Q and subsequent Annual Reports on Form 10-K, and all other information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, as updated by our subsequent filings under the Exchange Act. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Risks Relating to this Offering

If you purchase shares of our common stock sold in this offering, you may experience immediate and substantial dilution in the net tangible book value of your shares. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of 12,711,864 shares of our common stock are sold at a price of \$5.90 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on March 13, 2023, for aggregate gross proceeds of approximately \$75.0 million, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of \$1.48 per share. For a more detailed discussion of the foregoing, see the section titled “Dilution” below. To the extent outstanding stock options or pre-funded warrants are exercised or restricted stock units are settled, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then-existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

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

Our management has broad discretion in the application of the net proceeds from this offering, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Our management could spend the net proceeds from this offering in ways that do not improve our results of operations or enhance the value of our common stock. 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 securities 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.

The actual number of shares we will issue under the Sales Agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the Sales Agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Jefferies at any time throughout the term of the Sales Agreement. The number of shares that are sold by Jefferies after delivering a placement notice will fluctuate based on the market price of the common stock during the sales period and limits we set with Jefferies. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

The common stock offered hereby will be sold in “at the market offerings,” and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different levels of dilution and different outcomes in their investment results. We will have discretion,

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subject to market demand, to vary the timing, prices, and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid.

The number of shares of our common stock available for future issuance or sale could adversely affect the per share trading price of our common stock.

We cannot predict whether future issuances or sales of our common stock or the availability of shares for resale in the open market will decrease the per share trading price of our common stock. The issuance of substantial numbers of shares of our common stock in the public market or the perception that such issuances might occur could have an adverse effect on the per share trading price of our common stock.

CAUTIONARY 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, the impact of the ongoing 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 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 Part II, Item 1A, “Risk Factors,” in our Annual Report on Form 10-K for the fiscal year ended December 31, 2022, 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 may issue and sell shares of our common stock having aggregate sales proceeds of up to \$75.0 million from time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. There can be no assurance that we will sell any shares under or fully utilize the Sales Agreement with Jefferies as a source of financing.

We currently intend to use the net proceeds of this offering, if any, primarily for general corporate purposes, which may include funding research, preclinical and clinical development of our product candidates, increasing our working capital and capital expenditures. However, we have no current commitments or obligations to do so.

The expected net proceeds from this offering will not be sufficient for us to fund our current product candidates or any future product candidate through regulatory approval, and we will need to raise substantial additional capital to complete the development and commercialization of our current product candidates and any future product candidates. 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, the accompanying prospectus and the documents incorporated by reference herein and therein, as well as the amount of cash used in our operations. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds.

DILUTION

If you invest in our common stock, your ownership interest will be immediately diluted to the extent of the difference between the price per share you pay in this offering and the adjusted net tangible book value per share of our common stock immediately after this offering. The net tangible book value of our common stock as of December 31, 2022 was approximately \$195,437,137, or approximately \$4.08 per share of common stock based upon 47,899,031 shares outstanding as of December 31, 2022. Net tangible book value per share is determined by dividing our total tangible assets less our total liabilities by the number of shares of common stock outstanding.

After giving effect to the sale of our common stock in the aggregate amount of \$75.0 million at an assumed offering price of \$5.90 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on March 13, 2023, and after deducting commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of December 31, 2022, would have been \$267.9 million, or \$4.42 per share of common stock. This represents an immediate increase in net tangible book value of \$0.34 per share to our existing stockholders and an immediate dilution in net tangible book value of \$1.48 per share to new investors in this offering.

The following table illustrates this calculation on a per share basis. The as-adjusted information is illustrative only and will adjust based on the actual price to the public, the actual number of shares sold and other terms of the offering determined at the time shares of our common stock are sold pursuant to this prospectus supplement and the accompanying prospectus. The as-adjusted information assumes that all of our common stock in the aggregate amount of \$75.0 million is sold at the assumed offering price of \$5.90 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on March 13, 2023. The shares sold in this offering, if any, will be sold from time to time at various prices.

Assumed public offering price per share	\$5.90
Net tangible book value per share as of December 31, 2022	\$4.08
Increase in net tangible book value per share attributable to the offering	<u>\$0.34</u>
As adjusted net tangible book value per share as of December 31, 2022, after giving effect to the offering	<u>\$4.42</u>
Dilution per share to new investors participating in the offering	<u>\$1.48</u>

The number of shares of our common stock and non-voting common stock to be outstanding after this offering is based on 47,899,031 shares of common stock and non-voting common stock (of which 11,402,037 shares are non-voting common stock) outstanding as of December 31, 2022 (including 201,716 unvested restricted shares outstanding as of December 31, 2022) and excludes:

- 9,390,930 shares of common stock issuable upon the exercise of stock options outstanding as of December 31, 2022 under our 2016 Plan and our 2020 Plan, with a weighted average exercise price of \$12.08 per share;
- 2,680,178 shares of common stock issuable upon the exercise of stock options granted after December 31, 2022 under the 2020 Plan with an exercise price of \$7.02; and
- 6,449,187 shares of common stock reserved for future issuance as of December 31, 2022 under our stock-based compensation plans, consisting of (i) 5,139,028 shares of common stock reserved for future issuance under the 2020 Plan, and (ii) 1,310,159 shares of common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan.

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To the extent that outstanding options have been or may be exercised, any restricted stock units have been or may be settled, 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.

PLAN OF DISTRIBUTION

We have entered into the Sales Agreement with Jefferies, under which we may offer and sell up to \$75.0 million of our shares of common stock from time to time through Jefferies acting as agent. Sales of our shares of common stock, if any, under this prospectus supplement and the accompanying prospectus will be made by any method that is deemed to be an “at the market offering” as defined in Rule 415(a)(4) under the Securities Act.

Each time we wish to issue and sell shares of common stock under the Sales Agreement, we will notify Jefferies of the number of shares to be issued, the dates on which such sales are anticipated to be made, any limitation on the number of shares to be sold in any one day and any minimum price below which sales may not be made. Once we have so instructed Jefferies, unless Jefferies declines to accept the terms of such notice, Jefferies has agreed to use its commercially reasonable efforts consistent with its normal trading and sales practices to sell such shares up to the amount specified on such terms. The obligations of Jefferies under the Sales Agreement to sell our shares of common stock are subject to a number of conditions that we must meet.

The settlement of sales of shares between us and Jefferies is generally anticipated to occur on the second trading day following the date on which the sale was made. Sales of our shares of common stock as contemplated in this prospectus supplement will be settled through the facilities of The Depository Trust Company or by such other means as we and Jefferies may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

We will pay Jefferies a commission of up to 3.0% of the aggregate gross proceeds we receive from each sale of our shares of common stock. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. In addition, we have agreed to reimburse Jefferies for the fees and disbursements of its counsel, payable upon execution of the Sales Agreement, in an amount not to exceed \$75,000, in addition to certain ongoing disbursements of its legal counsel, unless we and Jefferies otherwise agree. We estimate that the total expenses for the offering, excluding any commissions or expense reimbursement payable to Jefferies under the terms of the Sales Agreement, will be approximately \$0.2 million. The remaining sale proceeds, after deducting any other transaction fees, will equal our net proceeds from the sale of such shares.

Jefferies will provide written confirmation to us before the open on The Nasdaq Global Select Market on the day following each day on which shares of common stock are sold under the Sales Agreement. Each confirmation will include the number of shares sold on that day, the aggregate gross proceeds of such sales and the proceeds to us.

In connection with the sale of the shares of common stock on our behalf, Jefferies will be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation of Jefferies will be deemed to be underwriting commissions or discounts. We have agreed to indemnify Jefferies against certain civil liabilities, including liabilities under the Securities Act. We have also agreed to contribute to payments Jefferies may be required to make in respect of such liabilities.

The offering of our shares of common stock pursuant to the Sales Agreement will terminate as permitted therein.

This summary of the material provisions of the Sales Agreement does not purport to be a complete statement of its terms and conditions. A copy of the Sales Agreement will be filed as an exhibit to a current report on Form 8-K filed under the Exchange Act and will be incorporated by reference in this prospectus supplement.

Jefferies and its affiliates may in the future provide various investment banking, commercial banking, financial advisory and other financial services for us and our affiliates, for which services they may in the future

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receive customary fees. In the course of its business, Jefferies may actively trade our securities for its own account or for the accounts of customers, and, accordingly, Jefferies may at any time hold long or short positions in such securities.

A prospectus supplement and the accompanying prospectus in electronic format may be made available on a website maintained by Jefferies, and Jefferies may distribute the prospectus supplement and the accompanying prospectus electronically.

LEGAL MATTERS

Fenwick & West LLP, San Francisco, California, will pass upon certain legal matters and the validity of the common stock offered hereby on our behalf. Jefferies LLC is being represented in connection with this offering by Cooley LLP, New York, New York.

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 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.

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

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.

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.

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

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.

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

- 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.



Up to \$75,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Jefferies

March 15, 2023
