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

**FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

PRELUDE THERAPEUTICS INCORPORATED
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

81-1384762
(IRS Employer
Identification No.)

**175 Innovation Boulevard
Wilmington, Delaware 19805
(302) 467-1280**
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Krishna Vaddi, Ph.D.
Chief Executive Officer
Prelude Therapeutics Incorporated
175 Innovation Boulevard
Wilmington, Delaware 19805
(302) 467-1280
(Name, address, including zip code, and telephone number, including area code, of agent for service)

From time to time after the effective date of this registration statement.

(Approximate date of commencement of proposed sale to the public)

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box:

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

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

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

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I. D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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

Large accelerated filer
Non-accelerated filer

Accelerated filer
Smaller reporting company
Emerging growth company

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

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

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

SUBJECT TO COMPLETION, DATED FEBRUARY 15, 2024

PROSPECTUS



Prelude Therapeutics Incorporated

**7,936,759 shares of Common Stock
Offered by the Selling Stockholders**

This prospectus relates to the offer and resale from time to time of up to 7,936,759 shares of our voting common stock, \$0.0001 par value per share, or 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 offer, sell or distribute 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 “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 commissions, discounts, brokerage fees and similar expenses, if any, attributable to their sales of shares of our common stock.

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 February 14, 2024, the last reported sales price for our common stock was \$3.38 per share. 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 shares of common stock covered by the prospectus supplement and any related free writing prospectus.

We are currently an “emerging growth company” and a “smaller reporting company” as defined under U.S. federal securities laws and, as such, have elected to comply with reduced public company reporting requirements. See “Prospectus Summary – Implications of Being an Emerging Growth Company and Smaller Reporting Company.” This prospectus complies with the requirements that apply to an issuer that is an emerging growth company and a smaller reporting company.

An investment in our shares of common stock involves a high degree of risk. You should carefully consider the information under the heading “[Risk Factors](#)” beginning on page 8 of this prospectus before investing in our shares of common stock.

The registration statement to which this prospectus relates registers the resale of a substantial number of our shares of common stock by the selling stockholders. Sales in the public market of a large number of shares of our common stock, or the perception in the market that holders of a large number of shares of our common stock intend to sell shares, could reduce the market price of our common stock.

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 , 2024

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 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, the selling stockholders may sell up to 7,936,759 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 shares of our common stock that the selling stockholders may offer. Each time the selling stockholders offer shares of our common stock under this prospectus, the selling stockholders will provide a prospectus supplement to the extent required, or if appropriate, a post-effective amendment to the registration statement of which this prospectus is part that will contain specific information about the terms of the offering. Any prospectus supplement may also add, update or change information contained in this prospectus or in documents we have incorporated by reference into 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. This prospectus, together with any applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to this offering. You should carefully read both this prospectus and any applicable prospectus supplement together with the additional information described under the headings “Where You Can Find More Information” and “Incorporation of Information by Reference” before buying any shares of our common stock in this offering.

You should rely only on the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. Neither we nor the selling stockholders 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 the selling stockholders take no responsibility for, and can provide no assurance as to the reliability of, any other information others may give you. If different information is given or different representations are made, you may not rely on that information or those representations as having been authorized by us or the selling stockholders. 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 shares of our common stock. This prospectus and any applicable prospectus supplement may only be used where it is legal to sell shares of our common stock.

THIS PROSPECTUS MAY NOT BE USED TO OFFER AND SELL SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT TO THE EXTENT SUCH PROSPECTUS SUPPLEMENT IS REQUIRED.

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.

This prospectus contains or incorporates by reference summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under “Where You Can Find More Information” and “Incorporation of Information by Reference.”

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This document contains or incorporates by reference documents containing references to trademarks, service marks and trade names owned by us or belonging to other entities. Solely for convenience, trademarks, service marks and trade names referred to in this document may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we or the applicable licensor will not assert, to the fullest extent under applicable law, our or its rights to these trademarks, service marks and trade names. The Company does not intend its use or display of other companies' trademarks, service marks or trade names to imply a relationship with, or endorsement or sponsorship of it by, any other companies. All trademarks, service marks and trade names included in this document are the property of their respective owners.

PROSPECTUS SUMMARY

This summary highlights information contained in other parts of this prospectus or incorporated by reference into this prospectus. This summary may not contain all the information that you should consider before investing in shares of our common stock. 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

Prelude Therapeutics Incorporated (“Prelude”) is 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, or NCEs, that we advance into clinical trials. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our steady progress in creating a wholly owned, internally developed pipeline. We also began work with our partner AbCellera Biologics, Inc. (“AbCellera”) on an early-stage discovery program involving potent degraders as payloads for novel antibodies targeting tumor specific antigens. 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 differentiated proprietary 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 including kinases, targeted protein degraders, and precision antibody drug conjugates. Our pipeline is designed to serve patients with high unmet medical need, where there are limited or no treatment options. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

The following table summarizes our product candidate pipeline:

PROGRAM	CANCER INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	Strategic Priorities
SMARCA2 PRT3789 (IV)	Patients with SMARCA4 mutated NSCLC and other cancers				Drive to POC in 2024
CDK9 PRT2527	Patients with B, T-cell malignancies and AML				Drive to POC in 2024
SMARCA2 (Oral)	Patients with SMARCA4 mutated NSCLC and other cancers				Target IND 1H 2024
SMARCA (Precision ADC)	Solid Tumors & Heme Malignancies not addressed by selective SMARCA2 degraders				Advance a Precision ADC Program with SMARCA Payload
New precision ADCs	Solid Tumors Heme Malignancies				Continue to build Precision ADC platform with novel payloads
Small Molecule Discovery	Solid Tumors Heme Malignancies				Advance a first-in-class small molecule program for a biomarker selected cancer

We have several drug candidates in clinical development and our objective is to generate proof-of-concept clinical data to guide our future regulatory pathways to approval. Our SMARCA2 molecule is a unique, first-in-class protein degrader, targeting specific patient populations. Our CDK9 inhibitor is selective and potent,

with a potentially superior safety profile over first-generation CDK9 inhibitors. Our next generation CDK4/6 inhibitor is specifically designed to be brain and tissue penetrant.

Our novel, first-in-class SMARCA2 degrader compounds and our potent, highly selective and potentially best-in-class CDK9 inhibitor represent our best opportunities for demonstrating clinical proof-of-concept in 2024 and advancing into potential Phase 2/3 registration studies. In 2023 we also announced a global partnership with AbCellera that will allow us to combine our small molecules and degraders expertise with their antibody expertise to develop precision antibody drug conjugates. We also intend to explore continued clinical development with external partners for our CDK4/6.

PRT3789 is a first-in-class, highly selective degrader of SMARCA2 protein, which along with SMARCA4, controls gene regulation through chromatin remodeling. Cancer cells with SMARCA4 mutations are dependent on SMARCA2 for their growth and survival and selectively degrading SMARCA2 induces cell death in cancer cells while sparing normal cells in preclinical models. PRT3789 has been shown to be efficacious and well tolerated in multiple preclinical models of SMARCA4 deleted/mutated cancers as monotherapy and in combination with standards of care therapies. We believe a selective SMARCA2 degrader has the potential to be of benefit in up to 10% of Non-Small Cell Lung cancer, or NSCLC, patients in the United States including many other tumor types with the SMARCA4 mutation.

Patients with SMARCA4 mutations or deletions have poor clinical outcomes and limited treatment options. Therefore, mutated or deleted SMARCA4 cancers provide a potential biomarker to select those patients most likely to respond to treatment with a highly selective SMARCA2 degrader.

PRT3789 is currently in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. To date, PRT3789 has completed the fifth dose escalation cohort and demonstrated selective, potent and dose dependent degradation of SMARCA2 with an acceptable safety profile. Based on PK/PD and safety data to date, the Company expects to conclude monotherapy dose escalation in the middle of 2024 and identify recommended phase 2 doses. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations has been initiated. Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in combination with docetaxel, evaluate efficacy, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into a registrational clinical trial. We expect to present initial data in the second half of 2024 from patients currently enrolled in the Phase 1 trial.

Our discovery team has identified a series of highly selective and orally bioavailable SMARCA2 degraders. The lead oral molecule, PRT7732, is currently in investigational new drug (IND) enabling studies and on track to enter Phase 1 clinical development in the second half of 2024. PRT7732 is structurally distinct from PRT3789 and in addition, may provide clinically meaningful differences, more patient-friendly dosing and may have utility in earlier lines of therapy.

As one of our first precision ADC programs, Prelude and our partner AbCellera began work on an early-stage discovery program involving potent degraders of the SMARCA family of proteins as payloads for novel antibodies targeting tumor specific antigens. Given the potent anti-tumor activity of these molecules in pre-clinical models of cancers beyond those targeted by our SMARCA2 selective degraders, we believe that these precision ADCs have the potential to extend the therapeutic utility of this class. The partnership includes up to five precision ADC targets. Under the terms of the agreement, Prelude and AbCellera will jointly discover, develop, and commercialize products emerging from the collaboration. AbCellera will lead manufacturing activities and Prelude will lead clinical development and global commercialization, subject to AbCellera's option to co-promote any resulting commercial products in the United States.

Our CDK9 candidate, PRT2527, is designed to be a potent and selective CDK9 inhibitor. We believe PRT2527 has the potential to avoid off-target toxicities, achieve substantial clinical activity and to become the best-in-class CDK9 inhibitor for hematologic malignancies.

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. PRT2527 has completed a Phase 1 multi-dose escalation study (NCT05159518) in patients with solid tumors. In this study, PRT2527 was shown to achieve high levels of target inhibition and the potential to be better tolerated than existing CDK9 inhibitors, specifically, managing neutropenia and an absence of meaningful gastrointestinal events or hepatotoxicity.

The observed dose-dependent downregulation of MYC and MCL1 mRNA expression, CDK9 transcriptional targets, was consistent with the degree of target engagement required for preclinical efficacy. As predicted by the preclinical models, 12 mg/m² QW dosing showed optimal target inhibition and has been selected as the optimal dose. The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530). In this study, PRT2527 is advancing in monotherapy hematological indications, such as B-cell malignancies and acute myeloid leukemia (AML), and it has initiated the combination with zanubrutinib in B-cell malignancies. We expect to complete the monotherapy dose escalation in B-cell malignancies in the middle of 2024. A second cohort of patients with AML is expected to initiate in the first half of 2024 in monotherapy.

Our MCL1 candidate, PRT1419, was designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. We concluded Phase 1 development of PRT1419 and established a confirmation dose in hematological malignancies. Based on the potential to address the intended patient population with the CDK9 inhibitor which potently inhibits MCL-1, we decided to prioritize our CDK9 inhibitor, PRT2527, and to discontinue development of PRT1419.

PRT3645 is a brain and tissue penetrant molecule that potently targets CDK4/6 with a biased selectivity for CDK4. A Phase 1 multi-dose escalation clinical trial of PRT3645 is underway with the objective of establishing a biologically active dose confirmation. At the 2023 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, we presented data, showing that treatment with PRT3645 was associated with a substantial decrease in pRb and Ki67 expression, indicating a high level of target engagement at the doses evaluated. Also, PRT3645 was generally well tolerated in the initial three dose cohorts of patients with no clinically meaningful gastrointestinal, hematologic or neurological events reported to date, leveraging its enhanced selectivity profile. We intend to complete the dose escalation portion of the Phase 1 clinical trial of PRT3645 this year and following its completion, to explore continued clinical development with external partners.

Corporate Information

We were formed under the laws of the State of Delaware in February 2016. Our principal executive offices are located at 175 Innovation Boulevard, Wilmington, Delaware, 19805, 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 shares of our common stock.

The Shares of Common Stock That May Be Offered

With this prospectus, the selling stockholders may offer and sell up to 7,936,759 shares of our common stock from time to time in one or more offerings as described in this prospectus. Each time the selling stockholders offer shares of our common stock with this prospectus, we will provide offerees with a prospectus supplement that will contain the specific terms of the shares of our common stock being offered, to the extent such prospectus supplement is required.

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

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

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

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

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

In addition, we are also a “smaller reporting company,” as defined in Rule 405 under the Securities Act. We may continue to be a smaller reporting company in any given year if either (i) the market value of our stock held by non-affiliates is less than \$250 million as of June 30 in the most recently completed fiscal year or (ii) our 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 registered for sale by Selling Stockholders	Up to 7,936,759 shares of our common stock that are issuable upon the exercise of certain pre-funded warrants.
Terms of the Offering	The selling stockholders will determine when and how they will dispose of the shares of common stock registered for resale under this prospectus.
Use of Proceeds	We will not receive any proceeds from the sale of shares of common stock by the selling stockholders.
Risk Factors	Before investing in our shares of common stock, you should carefully read and consider the information set forth in “ <i>Risk Factors</i> .”
Nasdaq ticker symbol	“PRLD”

For additional information concerning the offering, see the section of this prospectus titled “Plan of Distribution.”

RISK FACTORS

An investment in our shares of common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should carefully consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors,” in our Annual Report on Form 10-K for our most recently completed fiscal year, in any Quarterly Reports on Form 10-Q that have been filed since our most recent Annual Report on Form 10-K and in any other documents that we file (not furnish) with the SEC in the future, together with all of the other information appearing or incorporated by reference in this prospectus. See “Where You Can Find More Information” and “Incorporation of Information By Reference.” In addition, any prospectus supplement relating to an offering of our shares of common stock pursuant to this prospectus may contain a discussion of further risks applicable to an investment in our shares of common stock, which you should carefully consider prior to making a decision about investing in our shares of common stock. 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, any accompanying prospectus supplement and the documents incorporated by reference herein and therein contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events.

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

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in our Annual Report on Form 10-K for the most recently completed fiscal year, in any Quarterly Reports on Form 10-Q that have been filed since our most recent Annual Report on Form 10-K and in any other documents that we file (not furnish) to the SEC, as well as those discussed in this prospectus, any accompany prospectus supplement, the documents incorporated by reference into this prospectus or any accompanying prospectus supplement 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 the applicable prospectus supplement 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 shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement, the exhibits filed therewith or the documents incorporated by reference therein. For further information about us and the shares of common stock 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 we 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 access, free of charge, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act as soon as reasonably practicable after each such report is electronically filed with, or furnished to, the SEC.

Information about us is also available on 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. We have included our website address in this prospectus solely as an inactive textual reference.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” into this prospectus and any prospectus supplement information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents filed with the SEC. Any information referenced in this way is considered part of this prospectus. Any subsequent information filed with the SEC will automatically be deemed to update and supersede the information either contained, or incorporated by reference, into this prospectus, and will be considered part of this prospectus from the date those documents are filed. The information incorporated by reference is an important part of this prospectus.

We incorporate by reference in this prospectus the documents listed below that have been previously filed with the SEC as well as any filings made by us with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act from the initial filing of the registration statement of which this prospectus forms a part until the termination or completion of the offering of the shares of our common stock described in this prospectus:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2023, filed with the SEC on February 15, 2024;
- 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 4.5](#) to our Annual Report on Form 10-K for the year ended December 31, 2023; 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.

Notwithstanding the foregoing, information furnished under Items 2.02 and 7.01 of any Current Report on Form 8-K, including the related exhibits under Item 9.01, is not incorporated by reference in this prospectus or any prospectus supplement.

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, 175 Innovation Boulevard, Wilmington, Delaware, 19805, 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

The proceeds from the sale of the shares of common stock offered pursuant to this prospectus are solely for the accounts of the selling stockholders. Accordingly, we will not receive any of the proceeds from the sale of the shares of common stock offered by this prospectus. See “Selling Stockholders” and “Plan of Distribution” below.

The selling stockholders will pay any underwriting discounts and commissions and expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of the shares of common stock. We will bear the costs, fees and expenses incurred in effecting the registration of the shares of common stock covered by this prospectus, including all registration and filing fees, listing fees and fees and expenses of our counsel and our independent registered public accounting firm.

SELLING STOCKHOLDERS

This prospectus relates to the resale by the selling stockholders from time to time of up to 7,936,759 shares of our common stock pursuant to certain agreements between the Company and the selling stockholders, which provide the selling stockholders with certain registration rights. We are required to file this registration statement in accordance with our obligations set forth in the Registration Rights Agreement as more fully described in “Material Relationships with Selling Stockholders — Registration Rights Agreement.” The selling stockholders may from time to time offer and sell some, all or none of their shares of common stock set forth below pursuant to this prospectus and any accompanying prospectus supplement. As used in this prospectus, the term “selling stockholders” includes the persons listed in the table below, together with any additional selling stockholders listed in any subsequent amendment to this prospectus, and their pledgees, donees, transferees, distributees, assignees, successors, designees and others who later come to hold any of the selling stockholders’ interests in the common stock.

Except as set forth in the footnotes below, the following table sets forth, based on written representations from the selling stockholders, certain information as of the date hereof regarding the beneficial ownership of our common stock by the selling stockholders and the shares of common stock being offered by the selling stockholders. The applicable percentage ownership of common stock is based on 54,920,594 shares of common stock and non-voting common stock outstanding as of February 1, 2024. Information with respect to shares of common stock owned beneficially after the offering assumes the sale of all of the shares of common stock held by the selling stockholders or that may be acquired upon exercise of other securities.

We have determined beneficial ownership in accordance with the rules of the SEC. Except as indicated by the footnotes below, we believe, based on the information furnished to us, that the selling stockholders have sole voting and investment power with respect to all shares of common stock that they beneficially own, subject to applicable community property laws. Except as otherwise described below, based on the information provided to us by the selling stockholders, no selling stockholder is a broker-dealer or an affiliate of a broker dealer.

Holders of our common stock have no conversion rights. 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 amended and restated certificate of incorporation, or the Non-Voting Common Stock Beneficial Ownership Limitation. However, the Non-Voting Common Stock Beneficial 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. Holders of our pre-funded warrants have the right to exercise such pre-funded warrants for shares of our common stock, provided that as a result of such exercise, 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 4.99% of our common stock immediately following such exercise, or the Pre-Funded Warrant Beneficial Ownership Limitation, however, the Pre-Funded Warrant Beneficial Ownership Limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder upon 61 days’ notice to us.

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

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Please see the section titled “Plan of Distribution” for further information regarding the selling stockholders’ method of distributing these shares.

<u>Name of selling stockholders</u>	<u>Beneficial ownership before the offering</u>	<u>Number of shares of common stock being offered by selling stockholders</u>	<u>Beneficial ownership after the offering</u>	
	<u>Number of shares of common stock</u>		<u>Number of shares of common stock</u>	<u>%</u>
Baker Bros. Advisors LP and Affiliates(1)	10,222,968	7,936,759	10,222,968	18.61%

- (1) The shares reported under “Beneficial ownership before the offering” and “Beneficial ownership after the offering” consist of (i) 870,873 shares of common stock held by 667, L.P., or 667, (ii) 9,247,763 shares of common stock held by Baker Brothers Life Sciences, L.P., or Baker Brothers Life Sciences, and, together with 667, the Baker Funds, (iii) 5,188 shares of common stock held by Baker Bros. Advisors LP, or BBA, (iv) 41,500 shares of common stock issuable upon exercise of stock options held by Dr. Kelvin M. Neu, or the Neu Stock Options, and (v) 57,644 shares of common stock issuable upon exercise of stock options held by Julian C. Baker, or the Baker Stock Options. In addition, 667 holds 630,658 shares of non-voting common stock and pre-funded warrants to purchase 1,563,672 shares of common stock and Baker Brothers Life Sciences holds 6,539,415 shares of non-voting common stock and pre-funded warrants to purchase 17,968,343 shares of common stock. The rights of the Baker Funds to convert the shares of non-voting common stock held by them into common stock are subject to the Non-Voting Common Stock Beneficial Ownership Limitation and the rights of the Baker Funds to exercise the pre-funded warrants held by them for common stock are subject to the Pre-Funded Warrant Beneficial Ownership Limitation, accordingly the shares reported under “Beneficial ownership before the offering” and “Beneficial ownership after the offering” do not include any shares of common stock that may be acquired upon conversion of such shares of non-voting common stock or upon exercise of such pre-funded warrants. The shares of common stock registered hereby underlie pre-funded warrants acquired in a December 2023 private placement, or the December 2023 Private Placement, and consist of: (i) 593,452 shares of common stock underlying unexercised pre-funded warrants held by 667 and (ii) 7,343,307 shares of common stock underlying unexercised pre-funded warrants held by Baker Brothers Life Sciences. These pre-funded warrants acquired in the December 2023 Private Placement are subject to the Pre-Funded Warrant Beneficial Ownership Limitation, however the number of shares reported under “Number of shares of common stock being offered by selling stockholders” does not give effect to the Pre-Funded Warrant Beneficial Ownership Limitation. BBA is the management company and investment advisor to Baker Brothers Life Sciences and 667 and has sole voting and investment power with respect to the securities directly held by Baker Brothers Life Sciences and 667 and sole voting and investment power over the Neu Stock Options and the Baker Stock Options and the shares of common stock issuable upon exercise thereof. Baker Bros. Advisors (GP) LLC, or the GP, is the sole general partner of BBA. Julian C. Baker and Felix J. Baker are managing members of the GP. Julian C. Baker, Felix J. Baker, the GP and BBA may be deemed to be beneficial owners of the securities directly held by Baker Brothers Life Sciences and 667 and Julian C. Baker, Felix J. Baker and the GP may be deemed to be beneficial owners of the securities directly held or beneficially owned by BBA. Julian C. Baker, Felix J. Baker, the GP and BBA disclaim beneficial ownership of all securities held by Baker Brothers Life Sciences, 667, BBA, Dr. Kelvin M. Neu and Julian C. Baker except to the extent of their direct or indirect pecuniary interest therein. Julian C. Baker is also a member of the Company’s board of directors. The address for each of Julian C. Baker, Felix J. Baker, the GP, BBA and the Baker Funds is c/o Baker Bros. Advisors LP, 860 Washington Street, 3rd Floor, New York, NY 10014.

Material Relationships with Selling Stockholders

Below is a description of the material relationships in the past three years between the Company or any of its predecessors or affiliates and the selling stockholders.

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Board Membership

Julian Baker, a member of our board of directors, is affiliated with Baker Bros. Advisors LP and its affiliates.

May 2023 Underwritten Public Offering

In May 2023, the Company sold in an underwritten public offering 6,761,200 shares of its common stock and non-voting common stock, comprised of (i) 5,312,978 shares of its common stock and (ii) 1,448,222 shares of its non-voting common stock, at a price of \$5.75 per share, and to certain investors in lieu of common stock, the Company sold pre-funded warrants to purchase 12,895,256 shares of common stock at a price of \$5.7499 per pre-funded warrant. The Baker Funds purchased 1,448,222 shares of the Company's non-voting common stock and pre-funded warrants to purchase 11,595,256 shares of common stock in the offering.

December 2023 Private Placement

In December 2023, the Company entered into a securities purchase agreement with the Baker Funds, pursuant to which the Company sold in a private placement pre-funded warrants to purchase up to 7,936,759 shares of the Company's common stock at a price of \$3.1499 per warrant with an exercise price of \$0.0001 per share.

Registration Rights Agreement

In connection with the December 2023 Private Placement, the Company and the Baker Funds entered into an Amended and Restated Registration Rights Agreement, dated as of December 11, 2023, or the Baker Registration Rights Agreement, providing for the registration for resale of the shares of common stock underlying the pre-funded warrants sold in the December 2023 Private Placement.

PLAN OF DISTRIBUTION

The selling stockholders may, from time to time, offer and sell up to 7,936,759 shares in the aggregate of our common stock, which we refer to as the Selling Stockholders Shares, under this prospectus. 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 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 provisions 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

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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 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 Baker Registration Rights Agreement, 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 SECURITIES

The following description summarizes the most important terms of our capital stock, our amended and restated certificate of incorporation and our amended and 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 amended and restated certificate of incorporation and amended 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 amended and restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder of non-voting common stock upon 61 days' notice to us.

Dividend Rights

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

Voting Rights

Except as otherwise expressly provided in our amended and 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 amended and 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 amended and restated certificate of incorporation established a classified board of directors, to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No Preemptive or Similar Rights

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

Right to Receive Liquidation Distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock and our non-voting common stock and any participating preferred stock outstanding at that time, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights of and the payment of liquidation preferences, if any, on any outstanding shares of preferred stock.

Preferred Stock

We had no shares of preferred stock outstanding as of December 31, 2023.

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 the 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 December 31, 2023, we had outstanding options to purchase an aggregate 11,990,772 shares of our common stock, with a weighted average exercise price of \$10.63.

Warrants

May 2023 Pre-Funded Warrants

On May 18, 2023, we entered into an underwriting agreement with Morgan Stanley & Co. LLC as representative of the underwriters named therein pursuant to which we issued and sold in a public offering, among other securities, pre-funded warrants to purchase 12,895,256 shares of our common stock at a price of \$5.7499 per pre-funded warrant with an exercise price of \$0.0001 per share.

Each pre-funded warrant is immediately exercisable and will not expire. Under the terms of the pre-funded warrants, we may not effect the exercise of any such pre-funded warrant, and a holder will not be entitled to exercise any portion of any pre-funded warrant, if, upon giving effect to such exercise, the aggregate number of shares of common stock beneficially owned by the holder (together with its affiliates), other persons acting or who could be deemed to be acting as a group together with the holder or any of the holder's affiliates, and any other persons whose beneficial ownership of common stock would or could be aggregated with the holder's or any of the holder's affiliates for purposes of Section 13(d) or Section 16 of the Exchange Act would exceed 4.99% of the number of shares of common stock outstanding immediately after giving effect to the exercise (the "Maximum Percentage"), as such percentage ownership is calculated in accordance with Section 13(d) of the Exchange Act and the applicable regulations of the Securities and Exchange Commission (the "SEC"). A holder may reset the Maximum Percentage to a higher percentage (not to exceed 19.99%), effective 61 days after written notice to us, or a lower percentage, effective immediately upon written notice to us. Any such increase or decrease will apply only to that holder and not to any other holder of the pre-funded warrant.

December 2023 Pre-Funded Warrants

On December 11, 2023, we entered into a securities purchase agreement with certain institutional accredited investors, pursuant to which we agreed to issue and sell to in a private placement pre-funded warrants to purchase up to 7,936,759 shares of our common stock at a price of \$3.1499 per pre-funded warrant with an exercise price of \$0.0001 per share.

Each pre-funded warrant is immediately exercisable and will not expire. Under the terms of the pre-funded warrants, we may not effect the exercise of any such pre-funded warrant, and a holder will not be entitled to exercise any portion of any pre-funded warrant, if, upon giving effect to such exercise, the aggregate number of shares of common stock beneficially owned by the holder (together with its affiliates), other persons acting or who could be deemed to be acting as a group together with the holder or any of the holder's affiliates, and any other persons whose beneficial ownership of common stock would or could be aggregated with the holder's or any of the holder's affiliates for purposes of Section 13(d) or Section 16 of the Exchange Act would exceed the Maximum Percentage, as such percentage ownership is calculated in accordance with Section 13(d) of the Exchange Act and the applicable regulations of the SEC. A holder may reset the Maximum Percentage to a higher percentage (not to exceed 19.99%), effective 61 days after written notice to us, or a lower percentage, effective immediately upon written notice to us. Any such increase or decrease will apply only to that holder and not to any other holder of the pre-funded warrants.

Registration Rights

As of December 31, 2023, certain holders of shares of our common stock, non-voting common stock and pre-funded warrants are entitled to rights with respect to the registration of our common stock 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 investors rights agreement between us and the holders of these shares, or the IRA, which was entered into in connection with our redeemable convertible preferred stock financings prior to our IPO and under the terms of our registration rights agreements, or the Post-IPO RRAs, between us and with certain of our stockholders, or the RRA Investors.

Demand Registration Rights

Since 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

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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 Agreements

Pursuant to the Post-IPO RRAs between us and each of Baker Brothers and its affiliates, OrbiMed and its affiliates and Krishna 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 supplement 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

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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 RRAs require 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.

2023 Amended and Restated Registration Rights Agreement

In connection with our issuance of the December 2023 Pre-Funded Warrants, we amended and restated our registration rights agreement with Baker Brothers and its affiliates, pursuant to which we granted Baker Brothers and its affiliates certain demand, piggyback and resale shelf registration rights with respect to the shares of our common stock underlying the pre-funded warrants.

Anti-Takeover Provisions

The provisions of Delaware General Corporation Law, or DGCL, our amended and restated certificate of incorporation and our amended and restated bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of the 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.

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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 Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

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

- *Board of Directors Vacancies.* Our amended and restated certificate of incorporation and amended 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 amended and restated certificate of incorporation and amended and restated bylaws provide that our board of directors is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors.
- *Stockholder Action; Special Meetings of Stockholders.* Our amended and 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 amended and restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our amended and restated bylaws. Further, our amended and 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 amended and 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 amended and 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 the 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 amended and restated certificate of incorporation and amended and restated bylaws do not provide for cumulative voting.

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- *Directors Removed Only for Cause.* Our amended and restated certificate of incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of the holders of at least two-thirds of our outstanding common stock.
- *Amendment of Charter Provisions.* Any amendment of the above provisions in our amended and 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 amended and 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 amended and restated certificate of incorporation or our amended and 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 amended and 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.

LEGAL MATTERS

Fenwick & West LLP, Seattle, Washington, 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, 2023, 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.



7,936,759 Shares of Common Stock Offered by the Selling Stockholders

PROSPECTUS

, 2024

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following table sets forth estimated expenses in connection with the issuance and distribution of the shares of common stock being registered hereby.

	<u>Amount to be Paid</u>
SEC registration fee	\$ 3,315.25
FINRA filing fee	*
Printing and engraving*	*
Legal fees and expenses*	*
Accounting fees and expenses*	*
Transfer agent and registrar fees and expenses*	*
Miscellaneous expenses*	*
Total	<u>\$ *</u>

* Except for the SEC registration fee, estimated expenses are not presently known. The foregoing sets forth the general categories of expenses that we anticipate we will incur in connection with the offering of shares of common stock under this registration statement on Form S-3. To the extent required, any applicable prospectus supplement will set forth the estimated aggregate amount of expenses payable in respect of any offering of shares of common stock under the registration statement.

Discounts, concessions, commissions and similar selling expenses attributable to the sale of shares of our common stock covered by this prospectus will be borne by the selling stockholders. We will pay all expenses (other than discounts, concessions, commissions and similar selling expenses) relating to the registration of the shares with the SEC, as estimated in the table above.

Item 15. Indemnification of Directors and Officers

Section 145 of the Delaware General Corporation Law authorizes a court to award, or a corporation's board of directors to grant, indemnity to directors and officers under certain circumstances and subject to certain limitations. The terms of Section 145 of the Delaware General Corporation Law are sufficiently broad to permit indemnification under certain circumstances for liabilities, including reimbursement of expenses incurred, arising under the Securities Act of 1933, as amended, or the Securities Act.

As permitted by the Delaware General Corporation Law, the registrant's amended and restated certificate of incorporation contains a provision that eliminates, to the fullest extent permitted by law, the personal liability of a directors and officers for monetary damages resulting from breach of his or her fiduciary duties as a director or officer, except for liability:

- for any breach of the director's or officer's duty of loyalty to the registrant or its stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- under Section 174 of the Delaware General Corporation Law (regarding unlawful dividends, stock purchases or redemptions); or
- for any transaction from which the director derived an improper personal benefit.

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As permitted by the Delaware General Corporation Law, the registrant's amended and restated bylaws provide that:

- the registrant is required to indemnify its directors and officers to the fullest extent permitted by the Delaware General Corporation Law, subject to certain very limited exceptions;
- the registrant may indemnify its other employees and agents as set forth in the Delaware General Corporation Law;
- the registrant is required to advance expenses, as incurred, to its directors and officers in connection with a legal proceeding to the fullest extent permitted by the Delaware General Corporation Law, subject to certain very limited exceptions; and
- the rights conferred in the amended and restated bylaws are not exclusive.

The registrant has entered, and intends to continue to enter, into indemnification agreements with each of its directors and executive officers to provide these directors and executive officers additional contractual assurances regarding the scope of the indemnification set forth in the registrant's amended and restated certificate of incorporation and amended and restated bylaws and to provide additional procedural protections. At present, there is no pending litigation or proceeding involving a director or executive officer of the registrant for which indemnification is sought. The indemnification provisions in the registrant's amended and restated certificate of incorporation, amended and restated bylaws and the indemnification agreements entered into or to be entered into between the registrant and each of its directors and executive officers may be sufficiently broad to permit indemnification of the registrant's directors and executive officers for liabilities arising under the Securities Act.

The registrant currently carries liability insurance for its directors and officers.

ITEM Exhibits

16.

The exhibits listed below are filed (except where otherwise indicated) as part of this registration statement.

<u>Exhibit Number</u>	<u>Description of Document</u>	<u>Incorporated by Reference</u>				<u>Filed Herewith</u>
		<u>Form</u>	<u>File No.</u>	<u>Exhibit</u>	<u>Filing Date</u>	
3.1	Amended and Restated Certificate of Incorporation	10-Q	001-39527	3.1	8/3/2023	
3.2	Amended and Restated Bylaws	10-Q	001-39527	3.1	1/23/2023	
4.1	Form of Common Stock Certificate	S-1/A	333-248628	4.1	9/16/2020	
4.2	Amended and Restated Investors' Rights Agreement, dated August 21, 2020, by and among Prelude Therapeutics Incorporated and certain of its stockholders	S-1/A	333-248628	4.2	9/04/2020	
4.3	Amended and Restated Registration Rights Agreement, dated as of December 11, 2023, by and among Prelude Therapeutics Incorporated, 667, L.P., and Baker Brothers Life Sciences, L.P.	10-K	333-251874	4.4	2/15/2024	
4.4	Form of Pre-Funded Warrant	8-K	001-39527	4.1	12/11/2023	

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<u>Exhibit Number</u>	<u>Description of Document</u>	<u>Incorporated by Reference</u>				<u>Filed Herewith</u>
		<u>Form</u>	<u>File No.</u>	<u>Exhibit</u>	<u>Filing Date</u>	
10.1	Form of Securities Purchase Agreement, by and among Prelude Therapeutics Incorporated and certain Investors	10-K	001-39527	10.13	2/15/2024	
5.1	Opinion of Fenwick & West LLP					X
23.1	Consent of Ernst & Young LLP					X
23.2	Consent of Fenwick & West LLP (included in Exhibit 5.1)					X
24.1	Power of Attorney (included on the signature page hereto)					X
107	Filing Fee Table					

ITEM UNDERTAKINGS

17.

(a) The undersigned registrant hereby undertakes:

(1) to file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) to include any prospectus required by Section 10(a)(3) of the Securities Act;

(ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Securities and Exchange Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement; *provided, however*, that subparagraphs (i), (ii), and (iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Securities and Exchange Commission by the registrant pursuant to Section 13 or Section 15(d) of the Exchange Act that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act to any purchaser:

(i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

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(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided, however,* that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(5) That, for the purpose of determining liability of the registrant under the Securities Act to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

- (i) any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
- (iii) the portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and
- (iv) any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit, or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Wilmington, State of Delaware, on February 15, 2024.

PRELUDE THERAPEUTICS INCORPORATED

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

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Krishna Vaddi and Laurent Chardonnet, and each of them, as his or her true and lawful attorney-in-fact, proxy and agent, with full power of substitution, for him or her in any and all capacities, to sign any and all amendments to this registration statement (including pre-effective and post-effective amendments, any supplements, any abbreviated registration statement and any amendments thereto filed pursuant to Rule 462(b) increasing the number of securities for which registration is sought), and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact, proxies and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorney-in-fact, proxy and agent, or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Krishna Vaddi, Ph.D.</u> Krishna Vaddi, Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	February 15, 2024
<u>/s/ Laurent Chardonnet</u> Laurent Chardonnet	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	February 15, 2024
<u>/s/ Paul A. Friedman</u> Paul A. Friedman, M.D.	Director	February 15, 2024
<u>/s/ Martin Babler</u> Martin Babler	Director	February 15, 2024
<u>/s/ Julian Baker</u> Julian Baker	Director	February 15, 2024
<u>/s/ David Bonita</u> David Bonita, M.D.	Director	February 15, 2024
<u>/s/ Mardi C. Dier</u> Mardi C. Dier	Director	February 15, 2024
<u>/s/ Victor Sandor</u> Victor Sandor, M.D.C.M	Director	February 15, 2024



February 15, 2024

Prelude Therapeutics Incorporated
175 Innovation Boulevard
Wilmington, Delaware 19805

Ladies and Gentlemen:

At your request, we have examined the Registration Statement on Form S-3 filed by Prelude Therapeutics Incorporated, a Delaware corporation (the "**Company**"), with the Securities and Exchange Commission (the "**Commission**") on February 15, 2024 (the "**Registration Statement**"), in connection with the registration under the Securities Act of 1933, as amended (the "**Securities Act**"), of an aggregate of 7,936,759 shares of voting common stock, par value \$0.0001 per share (the "**Shares**"), for offer and resale by the selling stockholders described and listed in the Registration Statement (the "**Selling Stockholders**"), consisting of 7,936,759 Shares issuable by the Company to the Selling Stockholders upon the exercise of a currently outstanding pre-funded warrants to purchase Shares issued by the Company to the Selling Stockholders.

In connection with our opinion expressed below, we have also examined originals or copies of the prospectus prepared in connection with the Registration Statement (the "**Prospectus**"); the Company's current Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws (collectively, the "**Charter Documents**"); the Amended and Restated Registration Rights Agreement, dated as of December 11, 2023, by and among the Company, 667, L.P. and Baker Brothers Life Sciences, L.P.; the Pre-Funded Warrants, dated December 13, 2023 by and among the Company, 667, L.P. and Baker Brothers Life Sciences, L.P. (the "**Pre-Funded Warrant Agreements**"); certain corporate proceedings of the Company's board of directors and stockholders relating to the Registration Statement and the Charter Documents; and such other agreements, documents, certificates and statements of the Company, its transfer agent, its warrant agent and public or government officials, as we have deemed advisable, and have examined such questions of law as we have considered necessary. We have assumed the authenticity of all documents submitted to us as originals, the genuineness of all signatures on documents submitted to us, the conformity to originals of all documents submitted to us as copies, and the absence of any undisclosed termination, waiver or amendment to any document reviewed by us. In giving our opinion, we have also relied upon a good standing certificate issued by the Delaware Secretary of State and representations made to us by the Company, including representations that the Company has available a sufficient number of authorized Shares that are not currently outstanding or reserved for issuance under other outstanding securities or equity plans of the Company, to enable the Company to issue and deliver all of the Shares to be sold by the Selling Stockholders pursuant to the Registration Statement and the Prospectus.

We render this opinion only with respect to, and express no opinion herein concerning the application or effect of the laws of any jurisdiction other than, the existing Delaware General Corporation Law.

Based upon the foregoing, we are of the opinion that, the Shares that may be sold by the Selling Stockholders pursuant to the Registration Statement will, when delivered in the manner and for the consideration stated in the Registration Statement and the Prospectus, and when issued in accordance with the terms and conditions of the Pre-Funded Warrant Agreements, be validly issued, fully paid and nonassessable.

We consent to the use of this opinion as an exhibit to the Registration Statement and further consent to all references to us, if any, in the Registration Statement, the Prospectus and any amendments thereto. We do not thereby admit that we are within the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission thereunder. This opinion is intended solely for use in connection with sale of the securities to be sold by the Selling Stockholders pursuant to the Registration Statement and the Prospectus and is not to be relied upon for any other purpose. In providing this letter, we are opining only as to the specific legal issues expressly set forth above, and no opinion shall be inferred as to any other matter or matters. This opinion is rendered on, and speaks only as of, the date of this letter first written above, and does not address any potential change in facts or law that may occur after the date of this opinion letter. We assume no obligation to advise you of any fact, circumstance, event or change in the law or the facts that may hereafter be brought to our attention, whether or not such occurrence would affect or modify any of the opinions expressed herein.

Very Truly Yours,

/s/ Fenwick & West LLP

Fenwick & West LLP

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption “Experts” in the Registration Statement (Form S-3) and related Prospectus of Prelude Therapeutics Incorporated for the registration of 7,936,759 shares of its common stock and to the incorporation by reference therein of our report dated February 15, 2024, with respect to the financial statements of Prelude Therapeutics Incorporated included in its Annual Report (Form 10-K) for the year ended December 31, 2023, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Philadelphia, Pennsylvania
February 15, 2024

Calculation of Fee Filing Tables

Form S-3

(Form Type)

Prelude Therapeutics Incorporated

(Exact name of Registrant as Specified in its Charter)

Table 1 – Newly Registered Securities

Security Type	Security Class Title	Fee Calculation or Carry Forward Rule	Amount Registered ⁽¹⁾	Proposed Maximum Offering Price Per Unit	Maximum Aggregate Offering Price	Fee Rate	Amount of Registration Fee
Equity	Common stock, par value \$0.0001 per share	457(c)	7,936,759 ⁽²⁾	\$2.83 ⁽³⁾	\$22,461,027.97	\$0.00014760	\$3,315.25
	Total Offering Amounts						\$3,315.25
	Total Fees Previously Paid					—	—
	Total Fee Offsets					—	—
	Net Fee Due						\$3,315.25

- (1) Represents the shares of common stock, par value \$0.0001 per share (the “common stock”) of Prelude Therapeutics Incorporated (the “Registrant”) that will be offered for resale by the selling stockholders pursuant to the prospectus to which this exhibit is attached. Pursuant to Rule 416 under the Securities Act of 1933, as amended (the “Securities Act”), the shares being registered hereunder include such indeterminate number of additional shares of common stock as may be issuable as a result of stock splits, stock dividends or similar transactions with respect to the shares being registered hereunder.
- (2) Consists of an aggregate of 7,936,759 shares of the Registrant’s common stock issuable upon the exercise of pre-funded warrants of the Registrant.
- (3) The proposed maximum offering price per share has been estimated solely for the purpose of calculating the registration fee. The registration fee has been calculated in accordance with Rule 457(c) under the Securities Act based on the average high and low prices reported for the Registrant’s common stock on February 8, 2024.