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

SCHEDULE 13D

(Amendment No. 1)*

Under the Securities Exchange Act of 1934

Prelude Therapeutics Incorporated

(Name of Issuer)

COMMON STOCK

(Title of Class of Securities)

74065P101

(CUSIP Number)

OrbiMed Advisors LLC

OrbiMed Capital GP VI LLC

OrbiMed Capital LLC

**601 Lexington Avenue, 54th Floor
New York, NY 10022
Telephone: (212) 739-6400**

(Name, Address and Telephone Number of Person Authorized to
Receive Notices and Communications)

January 11, 2021

(Date of Event which Requires Filing of this Statement)

If the filing person has previously filed a statement on Schedule 13G to report the acquisition that is the subject of this Schedule 13D, and is filing this schedule because of §§240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box.

Note: Schedules filed in paper format shall include a signed original and five copies of the schedule, including all exhibits. See §240.13d-7(b) for other parties to whom copies are to be sent.

* The remainder of this cover page shall be filled out for a Reporting Person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter disclosures provided in a prior cover page.

The information required on the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

CUSIP No. 74065P101

1	Names of Reporting Persons. OrbiMed Advisors LLC	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) <input type="checkbox"/>	
6	Citizenship or Place of Organization Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 9,250,191 (1)
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 14,847,077 (1)
11	Aggregate Amount Beneficially Owned by Each Reporting Person 14,847,077 (1)	
12	Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions) <input type="checkbox"/>	
13	Percent of Class Represented by Amount in Row (11) 31.9% (2)	
14	Type of Reporting Person (See Instructions) IA	

(1) Includes 9,250,1921 voting shares of common stock of Prelude Therapeutics Incorporated (the "Issuer") and 5,596,886 non-voting shares of common stock of the Issuer. Each share of the Issuer's non-voting common stock is convertible into one share of the Issuer's voting common stock at the 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 the Issuer's common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in the Issuer's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by the holder of non-voting common stock upon 61 days' notice to the Issuer.

(2) This percentage is calculated based upon 46,578,400 shares of common stock outstanding of the Issuer, as reported by Bloomberg L.P. on January 11, 2021.

CUSIP No. 74065P101

1	Names of Reporting Persons. OrbiMed Capital GP VI LLC	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="radio"/> (b) <input type="radio"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) 0	
6	Citizenship or Place of Organization Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 9,250,191 (1)
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 14,847,077 (1)
11	Aggregate Amount Beneficially Owned by Each Reporting Person 14,847,077 (1)	
12	Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions) 0	
13	Percent of Class Represented by Amount in Row (11) 31.9% (2)	
14	Type of Reporting Person (See Instructions) OO	

(1) Includes 9,250,1921 voting shares of common stock of Prelude Therapeutics Incorporated (the "Issuer") and 5,596,886 non-voting shares of common stock of the Issuer. Each share of the Issuer's non-voting common stock is convertible into one share of the Issuer's voting common stock at the 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 the Issuer's common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in the Issuer's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by the holder of non-voting common stock upon 61 days' notice to the Issuer.

(2) This percentage is calculated based upon 46,578,400 shares of common stock outstanding of the Issuer, as reported by Bloomberg L.P. on January 11, 2021.

CUSIP No. 74065P101

1	Names of Reporting Persons. OrbiMed Capital LLC	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="radio"/> (b) <input type="radio"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) 0	
6	Citizenship or Place of Organization Cayman Islands	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 789,500
	8	Shared Voting Power 0
	9	Sole Dispositive Power 872,800
	10	Shared Dispositive Power 0
11	Aggregate Amount Beneficially Owned by Each Reporting Person 872,800	
12	Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions) 0	
13	Percent of Class Represented by Amount in Row (11) 1.9%*	
14	Type of Reporting Person (See Instructions) IA	

(1) Includes 789,500 voting shares of common stock of Prelude Therapeutics Incorporated (the "Issuer") and 83,300 non-voting shares of common stock of the Issuer. Each share of the Issuer's non-voting common stock is convertible into one share of the Issuer's voting common stock at the 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 the Issuer's common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in the Issuer's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by the holder of non-voting common stock upon 61 days' notice to the Issuer.

(2) This percentage is calculated based upon 46,578,400 shares of common stock outstanding of the Issuer, as reported by Bloomberg L.P. on January 11, 2021.

Item 1. Security and Issuer

This Amendment No. 1 (“Amendment No. 1”) to Schedule 13D supplements and amends the statement on Schedule 13D filed by OrbiMed Advisors LLC (“OrbiMed Advisors”), OrbiMed Capital GP VI LLC (“OrbiMed GP”), and OrbiMed Capital LLC (“OrbiMed Capital”) (collectively, the “Reporting Persons”) originally filed with the Securities and Exchange Commission (the “SEC”) on April 17, 2020. The Statement relates to the common stock, value \$.0001 per share (the “Shares”) of Prelude Therapeutics Incorporated, a corporation organized under the laws of Delaware (the “Issuer”), with its principal executive offices located at 200 Powder Mill Road, Wilmington, DE 19803. The Shares are listed on the NASDAQ Global Select Market under the ticker symbol “PRLD”. Information given in response to each item shall be deemed incorporated by reference in all other items, as applicable.

On January 11, 2021, the Issuer completed a public offering of 2,500,000 Shares at a price to the public of \$60.00 per Share (the “Offering”). In addition, the Issuer granted the underwriters an option exercisable for 30 days from the date of the Underwriting Agreement to purchase, at the public offering price less any underwriting discounts and commissions, up to an additional 375,000 Shares. As a result of the Offering, and the underwriters exercise of their option, and notwithstanding the participation of OrbiMed Private Investments VI, LP (“OPI VI”) and The Biotech Growth Trust PLC (“BIOG”) in the Offering, the Issuer’s total number of outstanding Shares increased to 46,578,400 (the “Outstanding Share Increase”). As a result of the Outstanding Share Increase, the percentage of outstanding Shares that the Reporting Persons may be deemed to beneficially own was reduced by more than 1% since the filing of the Statement.

Item 2. Identity and Background

(a) This Schedule 13D is being filed by OrbiMed Advisors LLC (“OrbiMed Advisors”), OrbiMed Capital GP VI LLC (“OrbiMed GP”), and OrbiMed Capital LLC (“OrbiMed Capital”) (collectively, the “Reporting Persons”).

(b) — (c), (f) OrbiMed Advisors, a limited liability company organized under the laws of Delaware and a registered investment adviser under the Investment Advisers Act of 1940, as amended, is the managing member or general partner of certain entities as more particularly described in Item 6 below. OrbiMed Advisors has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

OrbiMed GP, a limited liability company organized under the laws of Delaware, is the general partner of a limited partnership as more particularly described in Item 6 below. OrbiMed GP has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

OrbiMed Capital, a limited liability company organized under the laws of Delaware and a registered investment adviser under the Investment Advisers Act of 1940, as amended, is the investment adviser of certain entities as more particularly described in Item 6 below. OrbiMed Capital has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

The directors and executive officers of OrbiMed Advisors, OrbiMed Capital, and OrbiMed GP are set forth on Schedules I, II, and III, respectively, attached hereto. Schedules I, II and III set forth the following information with respect to each such person:

- (i) name;
 - (ii) business address;
 - (iii) present principal occupation of employment and the name, principal business and address of any corporation or other organization in which such employment is conducted; and
 - (iv) citizenship.
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(d) — (e) During the last five years, neither the Reporting Persons nor any Person named in Schedules I through III has been (i) convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors) or (ii) a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding was or is subject to a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, federal or state securities laws or finding any violation with respect to such laws.

Item 3. Source and Amount of Funds or Other Consideration

On and prior to the close of January 11, 2021, OrbiMed Advisors and OrbiMed GP, pursuant to their authority under the limited partnership agreement of OPI VI, as more particularly referred to in Item 6 below, caused OPI VI to purchase 41,700 non-voting Shares in the Offering.

On and prior to the close of January 11, 2021, OrbiMed Capital, as the investment advisor to BIOG, as more particularly referred to in Item 6 below, caused BIOG to purchase 83,300 non-voting Shares in the Offering.

The source of funds for such purchases was the working capital of OPI VI and BIOG.

Each non-voting Share is convertible into one voting Share at the 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 the Issuer's Shares immediately prior to and following such conversion, unless otherwise as expressly provided for in the Issuer's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by the holder of non-voting Shares upon 61 days' notice to the Issuer.

As a result of the transactions described in this Item 3, OrbiMed Advisors and OrbiMed GP may collectively be deemed to be the beneficial owners of approximately 31.9% of the outstanding Shares (including 24.8% of the voting Shares and 30.7% of the non-voting Shares) and OrbiMed Capital, as the investment advisor to BIOG and OrbiMed Partners Master Fund Limited ("OPM"), may be deemed to be the beneficial owner of 1.9% of the outstanding Shares (including 2.1% of the voting Shares and 0.7% of the non-voting Shares). OrbiMed GP, as the general partner of OPI VI, may be deemed to be the beneficial owner of approximately 31.9% of the outstanding Shares. OrbiMed Advisors, as the managing member of OrbiMed GP, may be deemed to be the beneficial owner of approximately 31.9% of the outstanding Shares. None of the Reporting Persons have acquired or disposed of any additional Shares since January 11, 2021.

Item 4. Purpose of Transaction

This statement relates to the acquisition of Shares by the Reporting Persons. The Shares acquired by the Reporting Persons were acquired for the purpose of making an investment in the Issuer and not with the intention of acquiring control of the Issuer's business on behalf of the Reporting Persons' respective advisory clients.

The Reporting Persons from time to time intend to review their investment in the Issuer on the basis of various factors, including the Issuer's business, financial condition, results of operations and prospects, general economic and industry conditions, the securities markets in general and those for the Issuer's Shares in particular, as well as other developments and other investment opportunities. Based upon such review, the Reporting Persons will take such actions in the future as the Reporting Persons may deem appropriate in light of the circumstances existing from time to time. If the Reporting Persons believe that further investment in the Issuer is attractive, whether because of the market price of Shares or otherwise, they may acquire Shares or other securities of the Issuer either in the open market or in privately negotiated transactions. Similarly, depending on market and other factors, the Reporting Persons may determine to dispose of some or all of the Shares currently owned by the Reporting Persons or otherwise acquired by the Reporting Persons either in the open market or in privately negotiated transactions.

Except as set forth in this Schedule 13D, the Reporting Persons have not formulated any plans or proposals which relate to or would result in: (a) the acquisition by any person of additional securities of the Issuer or the disposition of securities of the Issuer, (b) an extraordinary corporate transaction, such as a merger, reorganization or liquidation, involving the Issuer or any of its subsidiaries, (c) a sale or transfer of a material amount of the assets of the Issuer or any of its subsidiaries, (d) any change in the present Board of Directors or management of the Issuer, including any plans or proposals to change the number or term of directors or to fill any existing vacancies on the board, (e) any material change in the Issuer's capitalization or dividend policy of the Issuer, (f) any other material change in the Issuer's business or corporate structure, (g) any change in the Issuer's charter or bylaws or other instrument corresponding thereto or other action which may impede the acquisition of control of the Issuer by any person, (h) causing a class of the Issuer's securities to be deregistered or delisted from a national securities exchange or to cease to be authorized to be quoted in an inter-dealer quotation system of a registered national securities association, (i) a class of equity securities of the Issuer becoming eligible for termination of registration pursuant to Section 12(g)(4) of the Act or (j) any action similar to any of those enumerated above.

Item 5. Interest in Securities of the Issuer

(a) — (b) As of the date of this filing, OPI VI, a limited partnership organized under the laws of Delaware, holds 14,847,077 Shares, which amount includes 9,250,191 voting Shares and 5,596,886 non-voting Shares, constituting approximately 31.9% of the issued and outstanding Shares (including 24.8% of the voting Shares and 30.7% of the non-voting Shares). OrbiMed GP is the general partner of OPI VI, pursuant to the terms of the limited partnership agreement of OPI VI, and OrbiMed Advisors is the managing member of OrbiMed GP, pursuant to the terms of the limited liability company agreement of OrbiMed GP. As a result, OrbiMed Advisors and OrbiMed GP share power to direct the vote and disposition of the Shares held by OPI VI and may be deemed directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares held by OPI VI. OrbiMed Advisors exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein, each of whom disclaims beneficial ownership of the Shares held by OPI VI.

In addition, OrbiMed Advisors and OrbiMed GP, pursuant to their authority under the limited partnership agreement of OPI VI, caused OPI VI to enter into the agreements referred to in Item 6 below.

As of the date of this filing, BIOG, a publicly-listed investment trust organized under the laws of England, holds 346,500 Shares, which amount includes 263,200 voting Shares and 83,300 non-voting Shares, constituting approximately 0.7% of the issued and outstanding Shares (including 0.7% of the voting Shares and 0.7% of the non-voting Shares). OrbiMed Capital is the investment advisor of BIOG. As a result, OrbiMed Capital has the power to direct the vote and disposition of the Shares held by BIOG and may be deemed directly or indirectly, including by reason of mutual affiliation, to be the beneficial owner of the Shares held by BIOG. OrbiMed Capital disclaims any beneficial ownership over the shares of the other Reporting Persons. OrbiMed Capital exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein, each of whom disclaims beneficial ownership of the Shares held by BIOG.

Each non-voting Share is convertible into one voting Share at the 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 the Issuer's Shares immediately prior to and following such conversion, unless otherwise as expressly provided for in the Issuer's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by the holder of non-voting Shares upon 61 days' notice to the Issuer.

As of the date of this filing, OPM, an exempted company organized under the laws of Bermuda, holds 526,300 voting Shares constituting approximately 1.1% of the issued and outstanding Shares and 1.4% of the voting Shares. OrbiMed Capital is the investment advisor of OPM. As a result, OrbiMed Capital has the power to direct the vote and disposition of the Shares held by OPM and may be deemed directly or indirectly, including by reason of mutual affiliation, to be the beneficial owner of the Shares held by OPM. OrbiMed Capital disclaims any beneficial ownership over the shares of the other Reporting Persons. OrbiMed Capital exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein, each of whom disclaims beneficial ownership of the Shares held by OPM.

(c) Except as disclosed in Item 3, the Reporting Persons have not effected any transactions during the past sixty (60) days in any Shares.

(d) Not applicable.

(e) Not applicable.

Item 6. Contracts, Arrangements, Understandings or Relationships with Respect to Securities of the Issuer

In addition to the relationships between the Reporting Persons described in Items 2 and 5 above, OrbiMed GP is the general partner of OPI VI, pursuant to the terms of the limited partnership agreement of OPI VI. Pursuant to this agreement and relationship, OrbiMed GP has discretionary investment management authority with respect to the assets of OPI VI. Such authority includes the power to vote and otherwise dispose of securities held by OPI VI. The number of outstanding Shares of the Issuer attributable to OPI VI is 14,847,077 Shares. OrbiMed GP, pursuant to its authority under the limited partnership agreement of OPI VI, may be considered to hold indirectly 14,847,077 Shares.

OrbiMed Advisors is the managing member of OrbiMed GP, pursuant to the terms of the limited liability company agreement of OrbiMed GP. Pursuant to these agreements and relationships, OrbiMed Advisors and OrbiMed GP have discretionary investment management authority with respect to the assets of OPI VI. Such authority includes the power of OrbiMed GP to vote and otherwise dispose of securities held by OPI VI. The number of outstanding Shares attributable to OPI VI is 14,847,077 Shares. OrbiMed Advisors, pursuant to its authority under the terms of the limited liability company agreement of OrbiMed GP, may also be considered to hold indirectly 14,847,077 Shares.

OrbiMed Capital is the investment advisor to OPM and BIOG. OrbiMed Capital may be deemed to have voting and investment power over the securities held by OPM and BIOG. Such authority includes the power of OrbiMed Capital to vote and otherwise dispose of securities held by OPM and BIOG. The number of outstanding Shares attributable to OPM is 526,300 and to BIOG is 346,500 Shares. OrbiMed Capital, as the investment advisor to OPM and BIOG, may also be considered to hold indirectly 872,800 Shares.

David Bonita ("Bonita"), a member of OrbiMed Advisors, is a member of the Board of Directors of the Issuer and, accordingly, OrbiMed Advisors and OrbiMed GP may have the ability to affect and influence control of the Issuer. From time to time, Bonita may receive stock options or other awards of equity-based compensation pursuant to the Issuer's compensation arrangements for non-employee directors. Pursuant to an agreement with OrbiMed Advisors and OrbiMed GP, Bonita is obligated to transfer any securities issued under any such stock options or other awards, or the economic benefit thereof, to OrbiMed Advisors and OrbiMed GP, which will in turn ensure that such securities or economic benefits are provided to OPI VI.

Investors' Rights Agreement

In addition, OPI VI and certain other stockholders of the Issuer entered into an Amended and Restated Investors' Rights Agreement with the Issuer (the "Investors' Rights Agreement"), dated as of August 21, 2020. Pursuant to the Investors' Rights Agreement and subject to the terms and conditions therein, the parties agreed that:

Demand Registration Rights

At any time beginning six months following the date of the effective date of the registration statement of the IPO, the holders of at least 50% of the registrable securities then outstanding of the Issuer may make a written request that the Issuer register some or all of their registrable securities, subject to certain specified conditions and exceptions, including that the aggregated gross offering price of such offering must exceed \$10 million. The Issuer is required to use commercially reasonable efforts to effect the registration and will pay all registration expenses, other than underwriting discounts and commissions, related to any demand registration. The Issuer is not obligated to effect more than two of these registrations.

Piggyback Registration Rights

Whenever the Issuer proposes to file a registration statement under the Securities Act, including a registration statement on Form S-3 as discussed below, other than with respect to certain excluded registrations, OPI VI will be entitled to notice of the registration and have the right, subject to limitations that the underwriters may impose on the number of Shares included in the registration, to include the Shares held by OPI VI in the registration.

Form S-3 Registration Rights

At any time after the Issuer is qualified to file a registration statement on Form S-3 under the Securities Act, and subject to limitations and conditions specified in the Investors' Rights Agreement, holders of at least 25% of the registrable securities then outstanding may make a written request that the Issuer prepare and file a registration statement on Form S-3 covering their Shares, so long as the aggregate price to the public equal or exceeds \$5 million. The Issuer is not obligated to effect more than two of these Form S-3 registrations in any 12-month period.

Lock-Up Agreement

Pursuant to the Investors' Rights Agreement, OPI VI agreed that it will not, during the period ending 180 days after the date of the IPO (the "Lock-Up Period"), directly or indirectly (1) sell, assign, transfer, pledge, contract to sell, or otherwise dispose of, any Shares or securities convertible into or exercisable or exchangeable for Shares with respect to which OPI VI has or acquires the power of disposition or (2) enter into any swap or other agreement that transfers, in whole or in part, the economic risk of ownership of any such Shares.

After the Lock-Up Period expires, OPI VI's Shares will be eligible for sale in the public market, subject to any applicable limitations under Rule 144 under the Securities Act, and other applicable U.S. securities laws.

Offering Lock-Up Agreement

Pursuant to a lock-up agreement entered into in connection with the Offering (the "Offering Lock-Up Agreement"), each of OPI VI, OPM and BIOG agreed that it will not, during the period ending 180 days after the date of the Offering (the "Offering Lock-Up Period"), directly or indirectly (1) sell, assign, transfer, pledge, contract to sell, or otherwise dispose of, any Shares or securities convertible into or exercisable or exchangeable for Shares with respect to which OPI VI, OPM or BIOG, as applicable, has or acquires the power of disposition or (2) enter into any swap or other agreement that transfers, in whole or in part, the economic risk of ownership of any such Shares.

After the Offering Lock-Up Period expires, OPI VI's, OPM's and BIOG's Shares will be eligible for sale in the public market, subject to any applicable limitations under Rule 144 under the Securities Act, and other applicable U.S. securities laws.

The foregoing descriptions of the Investors' Rights Agreement and the Offering Lock-Up Agreement do not purport to be complete and are qualified in their entirety by reference to the full texts of the Investors' Rights Agreement and the Offering Lock-Up Agreement, which are filed as Exhibits 2 and 3 and incorporated herein by reference.

Item 7. Material to Be Filed as Exhibits

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital LLC, and OrbiMed Capital GP VI LLC.
2.	Amended and Restated Investors' Rights Agreement by and among the Issuer and each of the persons listed on Schedule A thereto, dated as of August 21, 2020 (incorporated by reference to Exhibit 4.2 to the Issuer's Registration Statement on Form S-1 (SEC 333-248628), filed with the SEC on September 4, 2020).
3.	Offering Lock-Up Agreement

Signature

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: January 13, 2021

ORBIMED ADVISORS LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

ORBIMED CAPITAL GP VI LLC

By: ORBIMED ADVISORS LLC, its managing member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

ORBIMED CAPITAL LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

SCHEDULE I

The names and present principal occupations of each of the executive officers and directors of OrbiMed Advisors LLC are set forth below. Unless otherwise noted, each of these persons is a United States citizen and has a business address of 601 Lexington Avenue, 54th Floor, New York, NY 10022.

<u>Name</u>	<u>Position with Reporting Person</u>	<u>Principal Occupation</u>
Carl L. Gordon	Member	Member OrbiMed Advisors LLC
Sven H. Borho German and Swedish Citizen	Member	Member OrbiMed Advisors LLC
Jonathan T. Silverstein	Member	Member OrbiMed Advisors LLC
W. Carter Neild	Member	Member OrbiMed Advisors LLC
Geoffrey C. Hsu	Member	Member OrbiMed Advisors LLC
C. Scotland Stevens	Member	Member OrbiMed Advisors LLC
David P. Bonita	Member	Member OrbiMed Advisors LLC
Trey Block	Chief Financial Officer	Chief Financial Officer OrbiMed Advisors LLC

SCHEDULE II

The names and present principal occupations of each of the executive officers and directors of OrbiMed Capital LLC are set forth below. Unless otherwise noted, each of these persons is a United States citizen and has a business address of 601 Lexington Avenue, 54th Floor, New York, NY 10022.

<u>Name</u>	<u>Position with Reporting Person</u>	<u>Principal Occupation</u>
Carl L. Gordon	Member	Member OrbiMed Capital LLC
Sven H. Borho German and Swedish Citizen	Member	Member OrbiMed Capital LLC
Jonathan T. Silverstein	Member	Member OrbiMed Capital LLC
W. Carter Neild	Member	Member OrbiMed Capital LLC
Geoffrey C. Hsu	Member	Member OrbiMed Capital LLC
C. Scotland Stevens	Member	Member OrbiMed Capital LLC
David P. Bonita	Member	Member OrbiMed Capital LLC
Trey Block	Chief Financial Officer	Chief Financial Officer OrbiMed Capital LLC

SCHEDULE III

The business and operations of OrbiMed Capital GP VI LLC are managed by the executive officers and directors of its managing member, OrbiMed Advisors LLC, set forth in Schedule I attached hereto.



EXHIBIT INDEX

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital LLC, and OrbiMed Capital GP VI LLC.
2.	Amended and Restated Investors' Rights Agreement by and among the Issuer and each of the persons listed on Schedule A thereto, dated as of August 21, 2020 (incorporated by reference to Exhibit 4.2 to the Issuer's Registration Statement on Form S-1 (SEC 333-248628), filed with the SEC on September 4, 2020).
3.	Offering Lock-Up Agreement

JOINT FILING AGREEMENT

The undersigned hereby agree that the Statement on Schedule 13D, dated January 12, 2021, with respect to the ordinary shares of Prelude Therapeutics Incorporated is filed on behalf of each of us pursuant to and in accordance with the provisions of Rule 13d-1(k) under the Securities Exchange Act of 1934, as amended. Each of the undersigned agrees to be responsible for the timely filing of this Statement, and for the completeness and accuracy of the information concerning itself contained therein. This Agreement may be executed in any number of counterparts, all of which taken together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the undersigned have executed this Agreement as of the 13th day of January 2021.

ORBIMED ADVISORS LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

ORBIMED CAPITAL GP VI LLC

By: ORBIMED ADVISORS LLC, its managing member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

ORBIMED CAPITAL LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

Morgan Stanley & Co. LLC
Goldman Sachs & Co. LLC
BofA Securities, Inc.

c/o Morgan Stanley & Co. LLC
1585 Broadway
New York, NY 10036

c/o Goldman Sachs & Co. LLC
200 West Street
New York, NY 10282

c/o BofA Securities, Inc.
One Bryant Park
New York, NY 10036

Ladies and Gentlemen:

The undersigned understands that Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC and BofA Securities, Inc. (collectively, the “**Representatives**”) propose to enter into an Underwriting Agreement (the “**Underwriting Agreement**”) with Prelude Therapeutics Incorporated, a Delaware corporation (the “**Company**”), providing for the public offering (the “**Public Offering**”) by the several Underwriters, including the Representatives (the “**Underwriters**”), of shares (the “**Shares**”) of the voting common stock, par value \$0.0001 per share, of the Company and the non-voting common stock, par value \$0.0001 per share, of the Company (together, the “**Common Stock**”).

To induce the Underwriters that may participate in the Public Offering to continue their efforts in connection with the Public Offering, the undersigned hereby agrees that, without the prior written consent of each of the Representatives, on behalf of the Underwriters, it will not, and will not publicly disclose an intention to, during the period commencing on the date hereof and ending 90 days after the date of the final prospectus (the “**Restricted Period**”) relating to the Public Offering (the “**Prospectus**”), (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of Common Stock beneficially owned (as such term is used in Rule 13d-3 of the Securities Exchange Act of 1934, as amended (the “**Exchange Act**”), by the undersigned or any other securities so owned convertible into or exercisable or exchangeable for Common Stock or (2) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the Common Stock, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise. The foregoing sentence shall not apply to:

(a) transactions relating to shares of Common Stock or other securities acquired in the Public Offering or in open market transactions after the completion of the Public Offering;

(b) transfers or dispositions of shares of Common Stock or any security convertible into or exercisable or exchangeable for Common Stock (i) as a bona fide gift or charitable contribution, (ii) by will or intestacy or to any member of the undersigned's immediate family or to a trust for the direct or indirect benefit of the undersigned and/or any member of the undersigned's immediate family, (iii) to any corporation, partnership, limited liability company or other business entity, all of the beneficial ownership interests of which, in each such case, are held by the undersigned or any member of the undersigned's immediate family, (iv) if the undersigned is an entity, to limited partners, members, shareholders or holders of similar equity interests in the undersigned, or (v) if the undersigned is an entity, to another corporation, partnership, limited liability company, trust or other business entity that is an affiliate (as defined in Rule 405 promulgated under the Securities Act of 1933, as amended) of the undersigned, or to any investment fund or other entity controlled or managed by the undersigned or affiliated with the undersigned; *provided* that, in the case of any transfer or distribution pursuant to this clause (b), (A) each transferee, donee or distributee shall sign and deliver a lock-up agreement substantially in the form of this agreement and (B) no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of Common Stock or any securities convertible into or exercisable or exchangeable for Common Stock shall be required or shall be voluntarily made during the Restricted Period (other than, in the case of a transfer or other disposition pursuant to clause (i) or (ii) above, a Form 5 required to be filed under the Exchange Act if the undersigned is subject to Section 16 reporting with respect to the Company under the Exchange Act; any such filing will indicate by footnote disclosure or otherwise the nature of the transfer or disposition); and *provided further* that any such transfer pursuant to this clause (b) shall not involve a transfer or distribution for value;

(c) transfers of shares of Common Stock or any security convertible into or exercisable or exchangeable for shares of Common Stock by operation of law pursuant to a qualified domestic order or other court order or in connection with a divorce settlement; *provided* that (i) any filing under Section 16(a) of the Exchange Act made during the Restricted Period shall clearly indicate in the footnotes thereto that (A) the filing relates to the circumstances described in this clause (c) and (B) no securities were sold by the undersigned, and (ii) the undersigned does not otherwise voluntarily effect any other public filing or report regarding such transfers during the Restricted Period;

(d) (i) the exercise of options or other similar awards or the vesting or settlement of awards granted pursuant to the Company's equity incentive plans as described in the Prospectus and outstanding on the date of the Underwriting Agreement (including the delivery and receipt of shares of Common Stock, other awards or any securities convertible into or exercisable or exchangeable for shares of Common Stock in connection with such exercise, vesting or settlement), or (ii) the transfer or disposition of shares of Common Stock or any securities convertible into shares of Common Stock by the undersigned to the Company (or the purchase and cancellation of the same by the Company) upon a vesting or settlement event of the Company's securities or upon the exercise of options to purchase the Company's securities on a "cashless" or "net exercise" basis solely to the extent permitted by the instruments representing such options pursuant to the Company's equity incentive plans as described in the Prospectus and solely to cover withholding tax obligations in connection with such transaction and any transfer to the Company for the payment of taxes as a result of such transaction, *provided* that (A) the shares of Common Stock received upon the exercise or settlement of the option are subject to the terms of this agreement, (B) no public disclosure or filing under Section 16(a) of the Exchange Act shall be voluntarily made during the Restricted Period and (C) to the extent a filing under Section 16(a) of the Exchange Act is required during the Restricted Period as a result of transfers in this clause (d), it shall clearly indicate that the filing relates to the circumstances described in this clause (d);

(e) transfers to the Company pursuant to the repurchase of shares of Common Stock in connection with the termination of the undersigned's employment with the Company or other service relationship with the Company pursuant to contractual agreements with the Company as in effect as of the date of the Prospectus, *provided* that no public disclosure or filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made during the Restricted Period;

(f) transactions in connection with the conversion of non-voting common stock to voting common stock, provided that any such shares of voting common stock received upon such conversion or reclassification shall be subject to the terms of this agreement;

(g) facilitating the establishment of a trading plan on behalf of a stockholder, officer or director of the Company pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of Common Stock, *provided* that (i) such plan does not provide for the transfer of Common Stock during the Restricted Period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required of or voluntarily made by or on behalf of the undersigned or the Company regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of Common Stock may be made under such plan during the Restricted Period; or

(h) transfers pursuant to a bona fide third-party tender offer for all outstanding shares of Common Stock or securities convertible into or exercisable or exchangeable for shares of Common Stock, merger, amalgamation, consolidation or other similar transaction approved by the Company's Board of Directors and made to all holders of the Company's securities involving a "change of control" of the Company (including, without limitation, the entering into any lock-up, voting or similar agreement pursuant to which the undersigned may agree to transfer, sell, tender or otherwise dispose of shares of Common Stock or other such securities in connection with such transaction, or vote any shares of Common Stock or other such securities in favor of any such transaction); *provided* that in the event that such tender offer, merger, amalgamation, consolidation or other such transaction is not completed, such securities held by the undersigned shall remain subject to the provisions of this agreement.

In addition, the undersigned agrees that, without the prior written consent of each of the Representatives, on behalf of the Underwriters, it will not, and will not publicly disclose an intention to, during the Restricted Period, make any demand for or exercise any right with respect to, the registration of any shares of Common Stock or any security convertible into or exercisable or exchangeable for Common Stock. The undersigned also agrees and consents to the entry of stop transfer instructions with the Company's transfer agent and registrar against the transfer of the undersigned's shares of Common Stock except in compliance with the foregoing restrictions.

For purposes of this agreement, (i) "immediate family" shall mean any relationship by blood, marriage, domestic partnership or adoption, not more remote than first cousin, and (ii) "change of control" shall mean the consummation of any bona fide third party tender offer, merger, amalgamation, consolidation or other similar transaction the result of which is that any "person" (as defined in Section 13(d)(3) of the Exchange Act), or group of persons, other than the Company, becomes the beneficial owner (as defined in Rules 13d-3 and 13d-5 of the Exchange Act) of greater than 50% of total voting power of all outstanding voting securities of the Company (or the surviving entity).

In the event that a release is granted to any Major Holder (as defined below) other than the undersigned relating to the lock-up restrictions set forth above for Common Stock, the same percentage of Common Stock held by the undersigned shall be immediately and fully released (the "**Pro-rata Release**") on the same terms from any remaining lock-up restrictions set forth herein. Notwithstanding the foregoing, no waiver or termination will constitute a Pro-rata Release, if: (a) such release is granted from such lockup restrictions to any individual party or parties (other than shareholders subject to Section 16 reporting with respect to the Company under the Exchange Act) to sell or otherwise transfer or dispose of Common Stock or other securities in an amount up to an aggregate of \$1,000,000, or (b) such waiver or termination, in full or in part, is in connection with any underwritten public offering, whether or not such offering or sale is wholly or partially a secondary offering of the Common Stock during the Restricted Period (a "**Follow-on Offering**"); provided that the undersigned, to the extent the undersigned has a contractual right to demand or require the registration of the undersigned's Common Stock or otherwise "piggyback" on a registration statement filed by the Company for the offer and sale of its Common Stock, (i) shall be offered the opportunity to participate on a pro rata basis consistent with such contractual rights in such Follow-on Offering and on pricing terms that are no less favorable than the terms of the Follow-on Offering or (ii) such contractual rights are waived pursuant to the terms thereof; and in the event the Underwriters make the determination to cut back the number of securities to be sold by shareholders in the Follow-on Offering, such cut back shall be on a basis consistent with such contractual rights. Notwithstanding any other provisions of this Agreement, if the Representatives in their sole discretion determine that a record or beneficial owner of Common Stock, or other securities convertible into or exercisable or exchangeable for Common Stock, should be granted an early Pro-rata Release, in an amount up to an aggregate of \$2,000,000, due to circumstances of emergency or hardship, then the undersigned shall not have any right to be granted a release pursuant to the terms of this paragraph.

In the event that any percentage of such Common Stock released from the lock-up restrictions are subject to any restrictions of the type set forth in clause (1) or (2) of the second paragraph of this Agreement, the same restrictions shall be applicable to the release of the same percentage of Common Stock held by the undersigned. In the event that the undersigned is released from any of its obligations under this Agreement (pursuant to this paragraph), or by virtue of this Agreement (pursuant to this paragraph), becomes entitled to offer, pledge, sell, contract to sell, or otherwise dispose of any Common Stock prior to the date that is 90 days after the date of the Prospectus, the Representatives shall use their commercially reasonable efforts to provide notification of such to the Company within three business days thereof, and the Company, in turn, shall use commercially reasonable efforts to notify the undersigned within one business day thereafter; provided that the failure to provide such notice to the Company or the undersigned shall not give rise to any claim or liability against the Representatives or the Underwriters. For purposes of this Agreement, each of the following persons is a “**Major Holder**”: each officer and director of the Company and each record or beneficial owner, as of the date hereof, of more than 1% of the outstanding shares of securities of the Company (for purposes of determining record or beneficial ownership of a shareholder, all shares of securities held by investment funds affiliated with such shareholders shall be aggregated).

The undersigned understands that the Company and the Underwriters are relying upon this agreement in proceeding toward consummation of the Public Offering. The undersigned further understands that this agreement is irrevocable and shall be binding upon the undersigned’s heirs, legal representatives, successors and assigns.

The undersigned acknowledges and agrees that the Underwriters have not provided any recommendation or investment advice nor have the Underwriters solicited any action from the undersigned with respect to the Public Offering of the Shares and the undersigned has consulted their own legal, accounting, financial, regulatory and tax advisors to the extent deemed appropriate. The undersigned further acknowledges and agrees that, although the Underwriters may provide certain Regulation Best Interest and Form CRS disclosures or other related documentation to you in connection with the Public Offering, the Underwriters are not making a recommendation to you to participate in the Public Offering or sell any Shares at the price determined in the Public Offering, and nothing set forth in such disclosures or documentation is intended to suggest that any Underwriter is making such a recommendation.

Whether or not the Public Offering actually occurs depends on a number of factors, including market conditions. Any Public Offering will only be made pursuant to an Underwriting Agreement, the terms of which are subject to negotiation between the Company and the Underwriters.

The undersigned understands that, if (i) the Representatives, on the one hand, or the Company, on the other hand, informs the other in writing, prior to the execution of the Underwriting Agreement, that it has determined not to proceed with the Public Offering, (ii) the Underwriting Agreement (other than the provisions thereof which survive termination) shall terminate or be terminated prior to payment for and delivery of the securities to be sold thereunder, (iii) the registration statement related to the Public Offering is withdrawn prior to the execution of the Underwriting Agreement or (iv) the Underwriting Agreement is not executed on or before February 26, 2021, then, in each case, this agreement shall automatically, and without any action on the part of any other party, be of no further force and effect, and the undersigned shall be automatically released from all obligations under this agreement.

This agreement and any claim, controversy or dispute arising under or related to this agreement shall be governed by and construed in accordance with the laws of the State of New York, without regard to the conflict of laws principles thereof.

[SIGNATURES TO FOLLOW]



By: _____

Name: David Bonita

Title: Director

ORBIMED PRIVATE INVESTMENTS VI, LP

By: OrbiMed Capital GP VI LLC,
its General Partner

By: OrbiMed Advisors LLC,
its Managing Member

By: _____

Name: David Bonita

Title: Member

ORBIMED PARTNERS MASTER FUND LIMITED

By: OrbiMed Capital LLC, solely in its
capacity as Investment Advisor

By: _____

Name: David Bonita

Title: Member

THE BIOTECH GROWTH TRUST PLC

By: OrbiMed Capital LLC, solely in its
capacity as Portfolio Manager

By: _____

Name: David Bonita

Title: Member
