

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

SCHEDULE 13D
(Rule 13d-102)

INFORMATION TO BE INCLUDED IN STATEMENTS FILED PURSUANT
TO RULE 13d-1(a) AND AMENDMENTS THERETO FILED PURSUANT
TO RULE 13d-2(a)

(Amendment No. 1)*

Prelude Therapeutics Incorporated

(Name of Issuer)

Common stock, par value \$0.0001 per share

(Title of Class of Securities)

74065P101

(CUSIP number)

Alexandra A. Toohey
Chief Financial Officer
Baker Bros. Advisors LP
860 Washington Street, 3rd Floor
New York, NY 10014
(212) 339-5690

(Name, address and telephone number of person authorized to receive notices and communications)

January 22, 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 Rule 13d-1(e), 13d-1(f) or 13d-1(g), check the following box .

(Continued on the following pages)

(Page 1 of 11 Pages)

*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 or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act.

1.	NAMES OF REPORTING PERSONS Baker Bros. Advisors LP		
2.	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP*		(a) <input type="checkbox"/> (b) <input type="checkbox"/>
3.	SEC USE ONLY		
4.	SOURCE OF FUNDS* OO		
5.	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 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: 10,126,417 (1)	
	8.	SHARED VOTING POWER: 0	
	9.	SOLE DISPOSITIVE POWER: 10,126,417 (1)	
	10.	SHARED DISPOSITIVE POWER: 0	
11.	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON: 10,126,417 (1)		
12.	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES* <input type="checkbox"/>		
13.	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 28.8% (1)(2)		
14.	TYPE OF REPORTING PERSON* IA, PN		

- (1) Includes 2,593 shares of voting common stock ("Common Stock") of Prelude Therapeutics Incorporated (the "Issuer") underlying options to purchase Common Stock of the Issuer ("Stock Options") and 5,188 shares of Common Stock directly held by the Adviser from Exercised Stock Options (as defined in Item 4).
- (2) Based on 35,176,344 shares of Common Stock of the Issuer outstanding as of January 11, 2021 as reported in the Issuer's Prospectus filed with the Securities and Exchange Commission ("SEC") on January 7, 2021, and the Issuer's press release issued on January 11, 2021, reflecting the exercise in full of the underwriter's overallotment option.

1.	NAMES OF REPORTING PERSONS Baker Bros. Advisors (GP) LLC		
2.	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP*		(a) <input type="checkbox"/> (b) <input type="checkbox"/>
3.	SEC USE ONLY		
4.	SOURCE OF FUNDS* OO		
5.	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 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: 10,126,417 (1)	
	8.	SHARED VOTING POWER: 0	
	9.	SOLE DISPOSITIVE POWER: 10,126,417 (1)	
	10.	SHARED DISPOSITIVE POWER: 0	
11.	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON: 10,126,417 (1)		
12.	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES* <input type="checkbox"/>		
13.	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 28.8% (2)		
14.	TYPE OF REPORTING PERSON* HC, OO		

- (1) Includes 2,593 shares of Common Stock of the Issuer underlying Stock Options and 5,188 shares of Common Stock directly held by the Adviser from Exercised Stock Options (as defined in Item 4).
- (2) Based on 35,176,344 shares of Common Stock of the Issuer outstanding as of January 11, 2021 as reported in the Issuer's Prospectus filed with the SEC on January 7, 2021, and the Issuer's press release issued on January 11, 2021, reflecting the exercise in full of the underwriter's overallotment option.

1.	NAMES OF REPORTING PERSONS Felix J. Baker		
2.	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP*		(a) <input type="checkbox"/> (b) <input type="checkbox"/>
3.	SEC USE ONLY		
4.	SOURCE OF FUNDS* OO		
5.	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(d) or 2(e) <input type="checkbox"/>		
6.	CITIZENSHIP OR PLACE OF ORGANIZATION United States		
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7.	SOLE VOTING POWER: 10,126,417 (1)	
	8.	SHARED VOTING POWER:	
	9.	SOLE DISPOSITIVE POWER: 10,126,417 (1)	
	10.	SHARED DISPOSITIVE POWER:	
11.	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON: 10,126,417 (1)		
12.	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES* <input type="checkbox"/>		
13.	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 28.8% (2)		
14.	TYPE OF REPORTING PERSON* IN, HC		

- (1) Includes 2,593 shares of Common Stock of the Issuer underlying Stock Options and 5,188 shares of Common Stock directly held by the Adviser from Exercised Stock Options (as defined in Item 4).
- (2) Based on 35,176,344 shares of Common Stock of the Issuer outstanding as of January 11, 2021 as reported in the Issuer's Prospectus filed with the SEC on January 7, 2021, and the Issuer's press release issued on January 11, 2021, reflecting the exercise in full of the underwriter's overallotment option.

1.	NAMES OF REPORTING PERSONS Julian C. Baker		
2.	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP*		(a) <input type="checkbox"/> (b) <input type="checkbox"/>
3.	SEC USE ONLY		
4.	SOURCE OF FUNDS* OO		
5.	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(d) or 2(e) <input type="checkbox"/>		
6.	CITIZENSHIP OR PLACE OF ORGANIZATION United States		
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7.	SOLE VOTING POWER: 10,126,417 (1)	
	8.	SHARED VOTING POWER	
	9.	SOLE DISPOSITIVE POWER: 10,126,417 (1)	
	10.	SHARED DISPOSITIVE POWER:	
11.	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON: 10,126,417 (1)		
12.	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES* <input type="checkbox"/>		
13.	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 28.8% (2)		
14.	TYPE OF REPORTING PERSON* IN, HC		

- (1) Includes 2,593 shares of Common Stock of the Issuer underlying Stock Options and 5,188 shares of Common Stock directly held by the Adviser from Exercised Stock Options (as defined in Item 4).
- (2) Based on 35,176,344 shares of Common Stock of the Issuer outstanding as of January 11, 2021 as reported in the Issuer's Prospectus filed with the SEC on January 7, 2021, and the Issuer's press release issued on January 11, 2021, reflecting the exercise in full of the underwriter's overallotment option.

Amendment No. 1 to Schedule 13D

This Amendment No. 1 to Schedule 13D amends and supplements the previously filed Schedules 13D filed by Baker Bros. Advisors LP (the “Adviser”), Baker Bros. Advisors (GP) LLC (the “Adviser GP”), Julian C. Baker, and Felix J. Baker (collectively the “Reporting Persons”). Except as supplemented herein, such statements, as heretofore amended and supplemented, remain in full force and effect.

The Adviser GP is the sole general partner of the Adviser. Pursuant to the management agreements, as amended, among the Adviser, Baker Brothers Life Sciences, L.P. (“Life Sciences”) and 667, L.P. (“667”, and together with Life Sciences, the “Funds”), and their respective general partners, the Funds’ respective general partners relinquished to the Adviser all discretion and authority with respect to the investment and voting power over securities held by the Funds, and thus the Adviser has complete and unlimited discretion and authority with respect to the Funds’ investments and voting power over investments.

All capitalized terms contained herein but not otherwise defined shall have the meanings ascribed to such terms in the Schedule 13D, as amended. Information given in response to each item shall be deemed incorporated by reference in all other items, as applicable.

Item 3. Source and Amount of Funds or Other Consideration

Item 3 of this Schedule 13D is supplemented and superseded, as the case may be, as follows:

The disclosure in Item 4 below is incorporated herein by reference.

Item 4. Purpose of the Transaction.

Item 4 of this Schedule 13D is supplemented and superseded, as the case may be, as follows:

On January 22, 2021, Dr. Kelvin M. Neu, a former full-time employee of the Adviser, resigned from the Board of Directors (the “Board”) of Prelude Therapeutics Incorporated (the “Issuer”) effective January 25, 2021. Effective on January 25, 2021, the Board appointed Julian C. Baker, a managing member of the Adviser GP, to fill the vacancy on the Board as a Class II Director. Julian C. Baker shall hold office for a term expiring at the 2022 Annual Meeting of the Issuer’s stockholders, which is the next stockholder meeting at which Class II directors will be elected. Julian C. Baker will also serve on the Issuer’s compensation committee and act as chairman of the Issuer’s nominating and governance committee. Dr. Neu, as compensation for his previous service on the Board, was granted 46,688 options (“Stock Options”) to purchase common stock (“Common Stock”), adjusted for a 1.1566 for 1 reverse split on September 18, 2020, which has an exercise price of \$12.85 and vests in 36 equal monthly installments beginning on October 24, 2020. Vesting of the Stock Options is subject to Julian C. Baker’s continuing service on the Board on each vesting date. The Stock Options expire on September 1, 2030. Dr. Neu previously served, and Julian C. Baker currently serves, on the Board, each as a representative of the Funds.

On January 27, 2021, the Adviser acquired beneficial ownership of 5,188 shares of Common Stock of the Issuer, as a result of the exercise of 5,188 of the Stock Options (the “Exercised Stock Options”) held directly by Dr. Neu. The policy of the Funds and the Adviser does not permit managing members of the Adviser GP or full-time employees of the Adviser to receive compensation for serving as directors of the Issuer, and the Funds are instead entitled to the pecuniary interest in the Exercised Stock Options. Dr. Neu, as a former full-time employee of the Adviser and former director of the Issuer, entered into a Nominee Agreement (the “Nominee Agreement”) with the Adviser on January 23, 2021. Pursuant to the Nominee Agreement, Dr. Neu agreed that, with respect to the Stock Options, the Exercised Stock Options and the Common Stock received as a result of the exercise of the Exercised Stock Options, the Adviser will have dispositive power as well as the ability to control the timing of exercise of the Exercised Stock Options and that any proceeds from the sale of the Common Stock will be remitted to the Adviser net of brokerage commissions consistent with the policies of the Adviser for current employees. Other than through their control of the Adviser, Felix J. Baker and Julian C. Baker have neither voting nor dispositive power and have no direct pecuniary interest in the Exercised Stock Options or the Common Stock. Pursuant to the Nominating Agreement, the Adviser funded Dr. Neu’s exercise of the Exercised Stock Options. The total amount expended on acquiring the Common Stock was \$66,665.80.

After giving effect to the exercise of the Exercised Stock Options, Dr. Neu holds 41,500 Stock Options, of which 2,593 are vested or will vest within 60 days hereof.

On January 6, 2021, the Issuer entered into an underwriting agreement (the “Underwriting Agreement”) with Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC, Barclays Capital, Inc. and BofA Securities (the “Underwriters”), related to a public offering (the “Offering”) of 2,583,334 shares of Common Stock and 291,666 shares of non-voting common stock (Non-Voting Common Stock”) of the Issuer at a price to the public of \$60.00 per share. 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 of Common Stock to cover overallocments, if any. The Offering closed on January 11, 2021.

Pursuant to the Offering, 667 and Life Sciences purchased 12,444 and 154,222 shares of Non-Voting Common Stock, respectively, at the offering price of \$60.00 per share, totaling 166,666 shares of Non-Voting Common Stock in the aggregate. Each of 667 and Life Sciences purchased the shares of Non-Voting Common Stock with their working capital.

Shares of Non-Voting Common Stock are convertible on a 1-for-1 basis at any time at the election of the holder into shares of Common Stock subject to beneficial ownership limitations as described below. The shares of Non-Voting Common Stock are only convertible to the extent that after giving effect to such conversion the holders thereof, together with their affiliates and any members of a Section 13(d) group with such holders, would beneficially own, for purposes of Rule 13d-3 under the Securities Exchange Act of 1934, as amended, no more than 9.99% of the outstanding shares of Common Stock (the “Beneficial Ownership Limitation”). By written notice to the Issuer, the Funds may from time to time increase or decrease the Beneficial Ownership Limitation applicable to that Fund to any other percentage not in excess of 19.99%. Any such change will not be effective until the 61st day after such notice is delivered to the Issuer. As a result of this restriction, the number of shares that may be issued upon conversion of the Non-Voting Common Stock by the above holders may change depending upon changes in the number of outstanding shares of Common Stock. The Non-Voting Common Stock is not currently convertible due to the effect of the Beneficial Ownership Limitation.

The Funds hold securities of the Issuer for investment purposes. The Reporting Persons or their affiliates may purchase additional securities or dispose of securities in varying amounts and at varying times depending upon the Reporting Persons’ continuing assessments of pertinent factors, including the availability of shares of Common Stock or other securities for purchase at particular price levels, the business prospects of the Issuer, other business investment opportunities, economic conditions, stock market conditions, money market conditions, the attitudes and actions of the Board and management of the Issuer, the availability and nature of opportunities to dispose of securities of the Issuer and other plans and requirements of the particular entities. . The Reporting Persons may discuss items of mutual interest with the Issuer’s management, other members of the Board and other investors, which could include items in subparagraphs (a) through (j) of Item 4 Schedule 13D.

Depending upon their assessments of the above factors, the Reporting Persons or their affiliates may change their present intentions as stated above and they may assess whether to make suggestions to the management of the Issuer regarding financing, and whether to acquire additional securities of the Issuer (by means of open market purchases, privately negotiated purchases, conversion of some or all of the Non-Voting Common Stock, or otherwise) or to dispose of some or all of the securities of the Issuer under their control.

Except as otherwise disclosed herein, at the present time, the Reporting Persons do not have any plans or proposals with respect to any extraordinary corporate transaction involving the Issuer including, without limitation, those matters described in subparagraphs (a) through (j) of Item 4 of Schedule 13D.

ITEM 5. Interest in Securities of the Issuer.

(a) and (b) Items 7 through 11 and 13 of each of the cover pages of this Amendment No. 1 are incorporated herein by reference.

The information set forth in Item 4 is hereby incorporated by reference into this Item 5.

Set forth below is the aggregate number of shares of Common Stock directly held by each of the Funds, which may be deemed to be indirectly beneficially owned by the Reporting Persons, as well as the shares of Common Stock that may be acquired upon conversion of Non-Voting Common Stock by the Funds, subject to the Beneficial Ownership Limitation.

Holder	Common Stock	Non-Voting Common Stock
667, L.P.	870,873	509,480
Baker Brothers Life Sciences, L.P.	9,247,763	5,212,371
Total	10,118,636	5,721,851

The Adviser holds 5,188 shares of Common Stock received as a result of the exercise of Exercised Stock Options.

The Adviser has voting and investment power over the Common Stock, Stock Options, Common Stock underlying such Stock Options and Common Stock received from the exercise of Stock Options by Julian C. Baker as directors' compensation. The Adviser GP, and Felix J. Baker and Julian C. Baker as managing members of the Adviser GP, may be deemed to have the power to vote or direct the vote of and the power to dispose or direct the disposition of the Common Stock, Stock Options, Common Stock received from the exercise of Stock Options and Common Stock underlying such Stock Options received by Julian C. Baker received as director's compensation.

The Adviser GP, Felix J. Baker and Julian C. Baker as managing members of the Adviser GP, and the Adviser may be deemed to be beneficial owners of securities of the Issuer directly held by the Funds.

(c) The information set forth in Items 3 and 4 is hereby incorporated by reference into this Item 5(c). Except as disclosed herein, none of the Reporting Persons or their affiliates has effected any other transactions in securities of the Issuer during the past 60 days.

(d) Certain securities of the Issuer are held directly by 667, a limited partnership the sole general partner of which is Baker Biotech Capital, L.P., a limited partnership the sole general partner of which is Baker Biotech Capital (GP), LLC. Julian C. Baker and Felix J. Baker are the controlling members of Baker Biotech Capital (GP), LLC.

Certain securities of the Issuer are held directly by Life Sciences, a limited partnership the sole general partner of which is Baker Brothers Life Sciences Capital, L.P., a limited partnership the sole general partner of which is Baker Brothers Life Sciences Capital (GP), LLC. Julian C. Baker and Felix J. Baker are the controlling members of Baker Brothers Life Sciences Capital (GP), LLC.

(e) Not applicable.

Item 6. Contracts, Arrangements, Understandings or Relationships with Respect to Securities of the Issuer.***Investors' Rights Agreement***

The Funds 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 offering price of such offering, net of selling expenses, 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, the Funds 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 of Common Stock included in the registration, to include shares of Common Stock held by the Funds 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, net of selling expenses, to the public equals 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, the Funds agreed that they will not, during the period ending 180 days after the date of the final prospectus related to the IPO (the "Lock-Up Period") (i.e., March 23, 2021), directly or indirectly (1) sell, assign, transfer, pledge, contract to sell, or otherwise dispose of, any shares of Common Stock or securities convertible into or exercisable or exchangeable for shares of Common Stock with respect to which the Funds have or acquire the power of disposition prior to the IPO, or (2) enter into any swap or other agreement that transfers, in whole or in part, the economic risk of ownership of any such share of Common Stock.

After the Lock-Up Period expires, the Funds' shares of Common Stock 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.

IPO Lock-Up Agreement

Pursuant to a lock-up agreement entered into with Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC, and BofA Securities, in connection with the IPO and dated July 23, 2020 (the "IPO Lock-Up Agreement"), and pursuant to the terms of the Investors Rights Agreement, each of the Funds agreed that it will not, during the Lock-Up Period, directly or indirectly (1) sell, assign, transfer, pledge, contract to sell, or otherwise dispose of, any shares of Common Stock or securities convertible into or exercisable or exchangeable for shares of Common Stock with respect to which the Funds, as applicable, has or acquires the power of disposition, other than securities purchased in or after the IPO; 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 of Common Stock.

After the IPO Lock-Up Period expires, the Funds' shares of Common Stock 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.

Post IPO Registration Rights Agreement

On December 15, 2020, the Issuer entered into a registration rights agreement (the "Registration Rights Agreement"). Under the Registration Rights Agreement, the Issuer agreed that, if at any time and from time to time, the Funds demand that the Issuer register securities directly held by them for resale under the Securities Act of 1933, as amended, the Issuer would be obligated to effect such registration and granted "piggyback" registration rights relating to a registration statement that registers securities for resale on behalf of another selling stockholder. The Issuer's registration obligations under the Registration Rights Agreement cover all securities now held or later acquired by the Funds, including securities issued or issuable upon the exercise or conversion of any other securities, will continue in effect for up to ten years as long as securities held by the Funds remain Registrable Securities (as defined in the Registration Rights Agreement), and include the Issuer's obligation to facilitate certain underwritten public offerings of securities by the Funds in the future, including no more than an aggregate of two underwritten public offerings per calendar year and a total of no more than two total underwritten public offerings.

The foregoing descriptions of the Investors' Rights Agreement, the IPO Lock-Up Agreement and the Registration Rights 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 IPO Lock-Up Agreement, and the Registration Rights Agreement which are filed as Exhibits 99.1, 99.2 and 99.3, respectively and incorporated herein by reference.

Item 7. Material to be Filed as Exhibits.

Exhibit	Description
<u>99.1</u>	<u>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).</u>
<u>99.2</u>	<u>Lock-Up Agreement by and among Morgan Stanley & Co. LLC, Goldman Sachs & Co. LLC, BofA Securities, Inc. and the Funds dated July 23, 2020.</u>
<u>99.3</u>	<u>Post IPO Registration Rights Agreement by and among the Issuer and the Funds dated December 20, 2020 (incorporated by reference to Exhibit 4.3 to the Issuer's Form S-1 filed with the SEC on January 4, 2021).</u>

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.

January 29, 2021

BAKER BROS. ADVISORS LP

By: Baker Bros. Advisors (GP) LLC, its general partner

By: /s/ Scott L. Lessing

Name: Scott L. Lessing

Title: President

BAKER BROS. ADVISORS (GP) LLC

By: /s/ Scott L. Lessing

Name: Scott L. Lessing

Title: President

/s/ Julian C. Baker

Julian C. Baker

/s/ Felix J. Baker

Felix J. Baker

FORM OF LOCK-UP AGREEMENT

July 23, 2020

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 common stock, par value \$0.0001 per share, of the Company (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 180 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 (other than issuer-directed shares of Common Stock purchased in the Public Offering by an officer or director of the Company) 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) transfers of shares of Common Stock or any security convertible into or exercisable or exchangeable for shares of Common Stock that are required to effect the recapitalization of the Company as described in the Prospectus and completed prior to the completion of the Public Offering, including the conversion of the outstanding preferred shares of the Company, *provided* that any shares of Common Stock received upon the exercise or exchange of any such convertible securities remain subject to the terms of this agreement;

(h) 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

(i) 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 75% of total voting power of all outstanding voting securities of the Company (or the surviving entity).

If the undersigned is an officer or director of the Company, the undersigned further agrees that the foregoing restrictions shall be equally applicable to any issuer- directed Shares the undersigned may purchase in the Public Offering.

If the undersigned is an officer or director of the Company, (i) each of the Representatives agrees that, at least three business days before the effective date of any release or waiver of the foregoing restrictions in connection with a transfer of shares of Common Stock, the Representatives will notify the Company of the impending release or waiver, and (ii) the Company will agree in the Underwriting Agreement to announce the impending release or waiver by press release through a major news service at least two business days before the effective date of the release or waiver. Any release or waiver granted by the Representatives hereunder to any such officer or director shall only be effective two business days after the publication date of such press release. The provisions of this paragraph will not apply if (a) the release or waiver is effected solely to permit a transfer not for consideration and (b) the transferee has agreed in writing to be bound by the same terms described in this agreement to the extent and for the duration that such terms remain in effect at the time of the transfer.

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 October 31, 2020 (provided that the Company may by written notice to the undersigned prior to October 31, 2020 extend such date for a period of up to an additional three months in the event that the Underwriting Agreement has not been executed by such date), 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.

Very truly yours,

IF AN ENTITY OR TRUST:

667, L.P

By: Baker Bros. Advisors LP, management company and investment advisor to **667, L.P.**, pursuant to authority granted to it by Baker Biotech Capital, L.P., general partner to **667, L.P.** and not as the general partner

By: /s/ Scott L. Lessing

Name: Scott L. Lessing

Title: President

BAKER BROTHERS LIFE SCIENCES, L.P.

By: Baker Bros. Advisors LP, management company and investment advisor to **Baker Brothers Life Sciences, L.P.**, pursuant to authority granted to it by Baker Brothers Life Sciences Capital, L.P., general partner to Baker Brothers Life Sciences, L.P., and not as the general partner

By: /s/ Scott L. Lessing

Name: Scott L. Lessing

Title: President

Scott L. Lessing

(Name)

860 Washington Street, 3rd Floor, New York, NY 10014

(Address)
