

| OMB APPROVAL | |
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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

Check this box to indicate that a transaction was made pursuant to a contract, instruction or written plan for the purchase or sale of equity securities of the issuer that is intended to satisfy the affirmative defense conditions of Rule 10b5-1(c). See Instruction 10.

| | | |
|--|---|---|
| 1. Name and Address of Reporting Person* BAKER BROS. ADVISORS LP (Last) (First) (Middle) 860 WASHINGTON STREET, 3RD FLOOR (Street) NEW YORK NY 10014 (City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol BICYCLE THERAPEUTICS PLC [BCYC] | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director <input checked="" type="checkbox"/> 10% Owner Officer (give title below) Other (specify below) |
| | 3. Date of Earliest Transaction (Month/Day/Year) 12/13/2024 | 6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person |
| 4. If Amendment, Date of Original Filed (Month/Day/Year) | | |

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

| 1. Title of Security (Instr. 3) | 2. Transaction Date (Month/Day/Year) | 2A. Deemed Execution Date, if any (Month/Day/Year) | 3. Transaction Code (Instr. 8) | | 4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5) | | | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) | 6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 7. Nature of Indirect Beneficial Ownership (Instr. 4) |
|---------------------------------|--------------------------------------|--|--------------------------------|---|---|------------|---------------------------|---|--|---|
| | | | Code | V | Amount | (A) or (D) | Price | | | |
| American Depositary Shares | 12/13/2024 | | P | | 2,809 | A | \$13.4979 ⁽¹⁾ | 790,763 | I | See Footnotes ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 30,241 | A | \$13.4979 ⁽¹⁾ | 8,666,247 | I | See Footnotes ⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 5,573 | A | \$13.6288 ⁽⁹⁾ | 796,336 | I | See Footnotes ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 59,995 | A | \$13.6288 ⁽⁹⁾ | 8,726,242 | I | See Footnotes ⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 22,722 | A | \$13.7242 ⁽¹⁰⁾ | 819,058 | I | See Footnotes ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 244,587 | A | \$13.7242 ⁽¹⁰⁾ | 8,970,829 | I | See Footnotes ⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 52,656 | A | \$13.804 ⁽¹¹⁾ | 871,714 | I | See Footnotes ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾ |
| American Depositary Shares | 12/13/2024 | | P | | 566,814 | A | \$13.804 ⁽¹¹⁾ | 9,537,643 | I | See Footnotes ⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾ |
| American Depositary Shares | 12/16/2024 | | P | | 42,369 | A | \$15.3418 ⁽¹²⁾ | 914,083 | I | See Footnotes ⁽²⁾⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾ |
| American Depositary Shares | 12/16/2024 | | P | | 457,631 | A | \$15.3418 ⁽¹²⁾ | 9,995,274 | I | See Footnotes ⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾ |

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

| 1. Title of Derivative Security (Instr. 3) | 2. Conversion or Exercise Price of Derivative Security | 3. Transaction Date (Month/Day/Year) | 3A. Deemed Execution Date, if any (Month/Day/Year) | 4. Transaction Code (Instr. 8) | | 5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5) | 6. Date Exercisable and Expiration Date (Month/Day/Year) | | 7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4) | 8. Price of Derivative Security (Instr. 5) | 9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4) | 10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 11. Nature of Indirect Beneficial Ownership (Instr. 4) |
|--|--|--------------------------------------|--|--------------------------------|---|--|--|-----|---|--|--|---|--|
| | | | | Code | V | | (A) | (D) | | | | | |

1. Name and Address of Reporting Person*
BAKER BROS. ADVISORS LP

 (Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

1. Name and Address of Reporting Person*
[667, L.P.](#)

(Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

1. Name and Address of Reporting Person*
[Baker Bros. Advisors \(GP\) LLC](#)

(Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

1. Name and Address of Reporting Person*
[Baker Brothers Life Sciences LP](#)

(Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

1. Name and Address of Reporting Person*
[BAKER FELIX](#)

(Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

1. Name and Address of Reporting Person*
[BAKER JULIAN](#)

(Last) (First) (Middle)
860 WASHINGTON STREET, 3RD FLOOR

(Street)
NEW YORK NY 10014

(City) (State) (Zip)

Explanation of Responses:

1. The price reported in Column 4 is a weighted average price. These American Depositary Shares ("ADS") of Bicycle Therapeutics plc (the "Issuer") were traded by 667, L.P. ("667") and Baker Brothers Life Sciences, L.P. ("Life Sciences", and together with 667, the "Funds") in multiple transactions at prices ranging from \$13.32 to \$13.50, inclusive. The reporting persons undertake to provide to the Issuer, any security holder of the Issuer, or the staff of the Securities and Exchange Commission (the "Staff"), upon request, full information regarding the number of shares traded at each separate price within the range set forth in this footnote.

2. After giving effect to the transactions reported herein and as a result of their ownership interest in (i) Baker Biotech Capital, L.P. and (ii) 667, Julian C. Baker and Felix J. Baker each may be deemed to have an indirect pecuniary interest in the ADS reported in column 5 of Table I held directly by or held for the benefit of 667, a limited partnership of which the sole general partner is Baker Biotech Capital, L.P., a limited partnership of which the sole general partner is Baker Biotech Capital (GP), LLC, due to their interest in 667 and Baker Biotech Capital, L.P.'s right to receive an allocation of a portion of the profits from 667.

3. Baker Bros. Advisors LP ("the Adviser") serves as the investment adviser to the Funds. In connection with the services provided by the Adviser, the Adviser receives an asset-based management fee that does not confer any pecuniary interest in the securities held directly by or held for the benefit of the Funds. Baker Bros. Advisors (GP) LLC (the "Adviser GP") is the Adviser's sole general partner. Julian C. Baker and Felix J. Baker are managing members of the Adviser GP. The Adviser has complete and unlimited discretion and authority with respect to the investment and voting power of the securities held directly by or held for the benefit of the Funds. The general partners of the Funds relinquished to the Adviser all discretion and authority with respect to the investment and voting power of the securities held directly by or held for the benefit of the Funds.

4. Julian C. Baker, Felix J. Baker, the Adviser GP and the Adviser disclaim beneficial ownership of the securities held directly by or held for the benefit of the Funds except to the extent of their pecuniary interest therein, and this report shall not be deemed an admission that any of Julian C. Baker, Felix J. Baker, the Adviser GP or the Adviser is a beneficial owner of such securities for purposes of Section

16 or any other purpose.

5. Includes beneficial ownership of 12,000 ADS issuable upon the vesting of restricted stock units (each an "RSU") payable solely in ADS previously issued to Felix J. Baker, in his capacity as a director of the Issuer pursuant to the Issuer's 2020 Equity Incentive Plan (the "2020 Plan") of which the Funds may be deemed to own a portion. The RSUs vest in three equal annual installments beginning on April 18, 2025, subject to Felix J. Baker's continuous service on the board of directors of the Issuer (the "Board") through the vesting date. Felix J. Baker serves on the Board as a representative of the Funds and their affiliates and control persons. Each RSU represents a contingent right to receive one Ordinary Share of the Issuer.

6. Pursuant to the policies of the Adviser, Felix J. Baker does not have any right to any of the Issuer's securities issued as compensation for his service on the Board and the Funds are entitled to an indirect proportionate pecuniary interest in the securities. The Funds each own an indirect proportionate pecuniary interest in the ADS received upon vesting of RSUs and non-qualified share options convertible solely into ADS of the Issuer ("Share Options") received as a result of his service on the Board. Solely as a result of their ownership interest in (i) the general partners of the Funds and (ii) the Funds, Felix J. Baker and Julian C. Baker may be deemed to have an indirect pecuniary interest in the ADS upon vesting of RSUs, Share Options, and ADS received upon the exercise of Share Options (i.e. no direct pecuniary interest) issued as compensation for such Board service.

7. The Adviser has voting and dispositive power over the Share Options, RSUs and any ADS received as a result of the exercise of Share Options or vesting of RSUs.

8. After giving effect to the transaction reported herein and as a result of their ownership interest in (i) Baker Brothers Life Sciences Capital, L.P. and (ii) Life Sciences, Julian C. Baker and Felix J. Baker may be deemed to have an indirect pecuniary interest in the ADS reported in column 5 of Table I held directly by or held for the benefit of Life Sciences, a limited partnership of which the sole general partner is Baker Brothers Life Sciences Capital, L.P., a limited partnership of which the sole general partner is Baker Brothers Life Sciences Capital (GP), LLC, due to their interest in Life Sciences and Baker Brothers Life Sciences Capital, L.P.'s right to receive an allocation of a portion of the profits from Life Sciences.

9. The price reported in Column 4 is a weighted average price. These shares were traded by 667 and Life Sciences in multiple transactions at prices ranging from \$13.42 to \$13.89, inclusive. The reporting persons undertake to provide to the Issuer, any security holder of the Issuer, or the Staff, upon request, full information regarding the number of shares traded at each separate price within the range set forth in this footnote.

10. The price reported in Column 4 is a weighted average price. These shares were traded by 667 and Life Sciences in multiple transactions at prices ranging from \$13.44 to \$13.81, inclusive. The reporting persons undertake to provide to the Issuer, any security holder of the Issuer, or the Staff, upon request, full information regarding the number of shares traded at each separate price within the range set forth in this footnote.

11. The price reported in Column 4 is a weighted average price. These shares were traded by 667 and Life Sciences in multiple transactions at prices ranging from \$13.48 to \$14.00, inclusive. The reporting persons undertake to provide to the Issuer, any security holder of the Issuer, or the Staff, upon request, full information regarding the number of shares traded at each separate price within the range set forth in this footnote.

12. The price reported in Column 4 is a weighted average price. These shares were traded by 667 and Life Sciences in multiple transactions at prices ranging from \$15.11 to \$15.49, inclusive. The reporting persons undertake to provide to the Issuer, any security holder of the Issuer, or the Staff, upon request, full information regarding the number of shares traded at each separate price within the range set forth in this footnote.

Remarks:

Felix J. Baker, a managing member of Baker Bros. Advisors (GP) LLC, the sole general partner of Baker Bros. Advisors LP, is a director of Bicycle Therapeutics plc (the "Issuer"). By virtue of their representation on the board of directors of the Issuer, for purposes of Section 16 of the Securities Exchange Act of 1934, as amended, the reporting persons other than Felix J. Baker are deemed directors by deputization of the Issuer.

By: Baker Bros. Advisors LP,
Name: Scott L. Lessing, Title: 12/17/2024
President /s/ Scott L. Lessing
Baker Bros. Advisors LP,
Mgmt. Co. and Inv. Adviser to
667, L.P., pursuant to
authority granted by Baker
Biotech Capital, L.P., GP to
667, L.P. Name: Scott L.
Lessing, Title: President /s/
Scott L. Lessing
12/17/2024

By: Baker Bros. Advisors
(GP) LLC, Name: Scott L.
Lessing, Title: President /s/
Scott L. Lessing
12/17/2024

Baker Bros. Advisors LP,
Mgmt. Co. and Inv. Adviser to
BAKER BROTHERS LIFE
SCIENCES, L.P., pursuant to
authority granted by Baker
Brothers Life Sciences
Capital, L.P., GP to Baker
Brothers Life Sciences, L.P.,
Name: Scott L. Lessing,
Title: President /s/
/s/ Felix J. Baker
12/17/2024

/s/ Julian C. Baker
12/17/2024

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.