

| OMB APPROVAL | |
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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

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

| | | |
|---|---|--|
| 1. Name and Address of Reporting Person* <u>Keen Nicholas</u> (Last) (First) (Middle) <u>C/O BICYCLE THERAPEUTICS PLC</u> <u>B900, BABRAHAM RESEARCH CAMPUS</u> (Street) <u>CAMBRIDGE X0 CB22 3AT</u> (City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol <u>BICYCLE THERAPEUTICS plc [BCYC]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Chief Scientific Officer</u> |
| | 3. Date of Earliest Transaction (Month/Day/Year) <u>01/03/2022</u> | |
| | 4. If Amendment, Date of Original Filed (Month/Day/Year) | 6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person |

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 | | | |
| Ordinary Shares | 01/03/2022 | | A | | 15,000 ⁽¹⁾ | A | \$0.00 ⁽²⁾ | 23,477 | D | |
| Ordinary Shares | | | | | | | | 7,000 | I | By GRAT |

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) | Date Exercisable | Expiration Date | | | | | | Title |
| Employee Stock Option (right to buy) | \$60.87 | 01/03/2022 | | A | | 30,000 | | (3) | 01/03/2032 | Ordinary Shares | 30,000 | \$0.00 | 30,000 | D | |

Explanation of Responses:

- Represents a restricted stock unit ("RSU") award. One-fourth (1/4) of the total number of RSUs shall vest on January 3, 2023 and the remaining RSUs shall vest in 12 equal quarterly installments thereafter.
- Each RSU represents a contingent right to receive one ordinary share.
- This option shall vest one-fourth (1/4) of the total number of shares underlying the option on January 3, 2023 and the remaining shares in 36 equal monthly installments thereafter.

Remarks:

/s/ Lee Kalowski, Attorney-in-Fact 01/05/2022

** 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.