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

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

September 7, 2022
Date of Report (Date of earliest event reported)

Bicycle Therapeutics plc
(Exact name of registrant as specified in its charter)

England and Wales	**001-38916**	**Not applicable**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

Blocks A & B, Portway Building, Granta Park Great Abington, Cambridge United Kingdom	**CB21 6GS**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **+44 1223 261503**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value £0.01 per share	n/a	The Nasdaq Stock Market LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.01 per share	BCYC	The Nasdaq Stock Market LLC

***** Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market LLC.

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events

On September 7, 2022, Bicycle Therapeutics plc (the "Company") issued a press release announcing BT5528 Phase I dose escalation results in patients with advanced solid tumors. A copy of the press release is filed as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated into this Item 8.01 by reference.

Also on September 7, 2022, the Company hosted a conference call and webcast to discuss the above-mentioned clinical trial results. A copy of the presentation used for the conference call and webcast was also posted to the Company's website. To access the presentation, investors should visit the "Presentation and Events" section of the Company's website at investors.bicycletherapeutics.com.

The information furnished under this Item 8.01 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or subject to the liabilities of that section. The information shall not be deemed incorporated by reference into any other filing with the Securities and Exchange Commission made by the Company, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Press Release dated September 7, 2022
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: September 7, 2022

BICYCLE THERAPEUTICS PLC

By: /s/ Lee Kalowski
Name: Lee Kalowski
Title: Chief Financial Officer

Exhibit 99.1

Bicycle Therapeutics Announces BT5528 Phase I Dose Escalation Results in Patients with Advanced Solid Tumors

Anti-tumor activity observed in heavily pre-treated patients with EphA2-positive ovarian and urothelial cancers; overall response rates of 22% (including one complete response) and 67%, respectively

Emergent safety profile of BT5528 suggests notable differentiation from current and prior generation EphA2 targeted molecules, with no treatment-related hemorrhage and low grade, low incidence of peripheral neuropathy, skin rash, and eye disorders

Enrollment in BT5528 expansion cohorts at the recommended Phase II dose (RP2D) of 6.5mg/m^2 every other week remains ongoing

Conference call scheduled for 8:30 a.m. ET

CAMBRIDGE, England, & BOSTON, September 7, 2022 – Bicycle Therapeutics plc (NASDAQ: BCYC), a biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (*Bicycle*®) technology, today announced Phase I dose escalation top-line results from its Phase I/II trial of BT5528, a BTC targeting EphA2, in patients with advanced solid tumors.

"The therapeutic profile from the dose escalation portion of the Phase I/II trial of BT5528 in patients with late-line disease suggests both differentiated safety and promising activity, most notably in ovarian and urothelial cancers," said Dominic Smethurst, Chief Medical Officer of Bicycle Therapeutics. "Significant safety concerns seen with antibody drug conjugate (ADC) approaches have limited the ability to effectively address EphA2, a target which correlates with tumor progression and is overexpressed in many cancers. Based on BT5528's promising and differentiated safety profile, we hope to demonstrate the true therapeutic potential of this target, this program and our broader Bicycle Toxin Conjugate (BTC®) platform."

"Smaller size, tumor penetration, pharmacokinetic and other qualities distinguish BT5528 and other members of our BTC platform from traditional toxin delivery systems and may confer significant advantages," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "Clinical data emerging from our BT5528 study continues to elucidate these potential advantages, and supports the continued, rapid advancement of our Bicycle-targeted therapeutics platform, all with the ultimate goal of creating unique, impactful medicines that transform the lives of patients. Enrollment continues on schedule in the expansion portion of this trial, and we anticipate providing further updates next year."

BT5528, a BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful, has demonstrated anti-tumor activity and differentiated tolerability. Bicycle has established an RP2D dose (6.5mg/m^2 every other week) and is enrolling ongoing expansion cohorts.

- **Preliminary signs of anti-tumor activity observed.** A total of 45 patients (15 at RP2D 6.5mg/m^2 every other week) were dosed with a median of four prior lines of therapy. Expression of EphA2 was evaluated retrospectively using an immunohistochemistry (IHC) assay.

    - Amongst these patients, anti-tumor activity was observed in urothelial and ovarian cancer patients.
    - A total of 21 ovarian cancer patients were dosed. Of these, nine response evaluable patients were determined to be EphA2-positive based on the IHC assay. The median prior lines of therapy for these nine patients was four.
    - Among these nine late-line ovarian cancer patients, six patients (67%) were observed to have a reduction in target lesions, including one patient with a complete response (CR) and one with a partial response (PR) under Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, resulting in a disease control rate (DCR) of 67% and an overall response rate (ORR) of 22%.
    - A total of eight urothelial patients were dosed. Of these, three response evaluable patients were determined to be EphA2-positive based on the IHC assay and of these three patients, two were observed to have tumor reductions constituting a PR under RECIST version 1.1 (ORR and DCR of 67%).

- **BT5528 well-tolerated at RP2D of 6.5mg/m^2 every other week**. Low, or no, levels of incidence of neutrophil count decrease, peripheral neuropathy, skin rash and eye disorders were reported. Low-grade GI treatment-related events were those most commonly reported amongst the 15 patients at this dose. There were three Grade 3 and above events at the RP2D: diarrhea (n=1, 7%) and anemia (n=2, 13%). In addition, and in contrast to the toxicities observed with EphA2 ADCs, Bicycle has observed no signs of treatment-related coagulopathy to date in any patient.

- **Bicycle advancing BT5528 in ongoing expansion cohorts.** In June 2022, Bicycle announced the dosing of the first patient in the part B dose expansion portion of the Phase I/II trial. Up to 56 patients will be enrolled in the initial expansion cohorts, with the ability to further expand enrollment based on results from these cohorts. Dose expansion is taking place in urothelial (n=14) and ovarian (n=14) cancers as well as in a basket cohort of other solid tumors (n=28), including non-small cell lung, triple-negative breast, head and neck, and esophageal cancers.

Conference Call Details

Bicycle Therapeutics will host a conference call and webcast today, September 7, 2022, at 8:30 a.m. ET to review the BT5528 trial data. To access the call, please dial (877) 870-4263 (domestic) or (412) 317-0790 (international) at least 10 minutes prior to the start time and ask to be joined to the Bicycle Therapeutics call. A live webcast of the presentation will be available on the Investors & Media section of the Bicycle website, bicycletherapeutics.com.

About Bicycle Therapeutics

Bicycle Therapeutics (NASDAQ: BCYC) is a clinical-stage biopharmaceutical company developing a novel class of medicines, referred to as Bicycles, for diseases that are underserved by existing therapeutics. Bicycles are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making Bicycles attractive candidates for drug development. Bicycle is evaluating BT5528, a second-generation Bicycle Toxin Conjugate (BTC®) targeting EphA2; BT8009, a second-generation BTC targeting Nectin-4, a well-validated tumor antigen; and BT7480, a Bicycle TICA® targeting Nectin-4 and agonizing CD137, in company-sponsored Phase I/II trials. In addition, BT1718, a BTC that targets MT1-MMP, is being investigated in an ongoing Phase I/IIa clinical trial sponsored by the Cancer Research UK Centre for Drug Development. Bicycle is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Lexington, Massachusetts. For more information, visit bicycletherapeutics.com.

Forward Looking Statements

This press release may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “seeks,” “will” and variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding the clinical development of BT5528 or any of Bicycle’s other product candidates or programs; the expected design and anticipated progression of and data readouts from Bicycle’s clinical trials of BT5528; the safety, tolerability or efficacy of BT5528; and the potential benefits of BT5528 or any of Bicycle’s other product candidates. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: risks to site initiation, clinical trial commencement, patient enrollment and follow-up, as well as to Bicycle’s abilities to meet other anticipated deadlines and milestones, presented by the ongoing COVID-19 pandemic; uncertainties inherent in the completion of clinical trials and clinical development of BT5528 and Bicycle’s other product candidates; availability and timing of results from clinical trials; whether initial or interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; the risk that trials and studies may be delayed and may not have satisfactory outcomes; expectations for regulatory approvals to conduct trials or to market product; and other important factors, any of which could cause Bicycle’s actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled “Risk Factors” in Bicycle’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 4, 2022, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether because of any new information, future events, changed circumstances or otherwise, except as may be required by law.

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