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

January 13, 2025
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 7.01 Regulation FD Disclosure

On January 13, 2025, Bicycle Therapeutics, plc (the "Company") issued a press release announcing updated topline zelenectide pevedotin data and highlighting 2025 strategic priorities and milestones.

A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein. The information furnished under this Item 7.01, including Exhibit 99.1, 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 SEC made by the Company, regardless of any general incorporation language in such filing.

Item 8.01 Other Events

On January 13, 2025, the Company announced updated topline results, current as of the data cut-off on January 3, 2025, from its ongoing Phase 1 Duravelo-1 trial evaluating zelenectide pevedotin. The updated topline results evaluating zelenectide pevedotin 5 mg/m^2 weekly plus pembrolizumab 200 mg once every three weeks in 22 first-line cisplatin-ineligible patients with mUC showed:

- 65% overall response rate (ORR) (13/20) among all efficacy-evaluable patients, and a 50% ORR (10/20) among patients with confirmed responses. Of the 3 unconfirmed responses, 1 patient remained on treatment at the time of the data cut.
- Median duration of response (mDOR) is not yet mature, with 12 patients still on treatment at the time of the data cut.
- Safety and tolerability profile continues to be broadly consistent with other Phase 1 zelenectide pevedotin monotherapy and combination cohorts. Adverse events of clinical interest such as peripheral neuropathy, skin reactions and eye disorders were primarily low grade. All cases of Grade 3 treatment-related adverse events (TRAEs) of clinical interest were reversible, and there were no Grade 4 or Grade 5 TRAEs of clinical interest. Notably, no patients withdrew from the study due to zelenectide TRAEs.

Item 9.01 Financial Statements and Exhibits

(a) Exhibits

99.1	Press Release dated January 13, 2025
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: January 13, 2025

BICYCLE THERAPEUTICS PLC

By: /s/ Alethia Young
Name: Alethia Young
Title: Chief Financial Officer

Exhibit 99.1

Bicycle Therapeutics Announces Updated Topline Zelenectide Pevedotin Data and Highlights 2025 Strategic Priorities and Milestones

Updated topline Phase 1 combination data for zelenectide pevedotin plus pembrolizumab continue to show promising anti-tumor activity and a differentiated safety profile in first-line cisplatin-ineligible metastatic urothelial cancer

NECTIN4 gene amplification development strategy underway for zelenectide pevedotin in breast cancer, lung cancer and multiple tumors, with several Phase 1/2 trials planned to start in 2025

Emerging radiopharmaceuticals pipeline progressing, with additional MT1-MMP human imaging data expected in mid-2025 and first EphA2 human imaging data planned for 2H 2025

Expected financial runway into 2H 2027 to support execution of clinical and strategic priorities

CAMBRIDGE, England & BOSTON, Jan. 13, 2025 – Bicycle Therapeutics plc (NASDAQ: BCYC), a pharmaceutical company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle®) technology, today announced updated topline Phase 1 combination data for zelenectide pevedotin plus pembrolizumab in previously untreated (first-line) cisplatin-ineligible patients with metastatic urothelial cancer (mUC). The company also announced recent accomplishments and outlined strategic priorities and anticipated milestones for 2025.

"Bicycle Therapeutics made significant advances across all aspects of our business in 2024. Notably, we drove important clinical progress of our targeted therapeutics in solid tumors, including greatly expanding the number of patients who could potentially benefit from our lead therapy zelenectide pevedotin, advanced our emerging pipeline of novel radiopharmaceuticals and strengthened our financial position and operational capabilities to advance our strategic priorities," said CEO Kevin Lee, Ph.D. "We are encouraged by our updated topline Phase 1 combination data for zelenectide pevedotin plus pembrolizumab in first-line cisplatin-ineligible patients, which we believe continue to demonstrate a differentiated safety profile and encouraging response rates in patients with poor prognosis and limited treatment options. We believe we are well-positioned to continue our strong momentum of execution over the course of 2025, which will be another year of important data milestones across our pipeline as we work to develop potentially transformative treatments that will help patients live longer and live well."

Updated Topline Zelenectide Pevedotin Plus Pembrolizumab Combination Data in First-Line mUC Highlights

Zelenectide pevedotin, a Bicycle® Toxin Conjugate (BTC®), has significant potential to treat Nectin-4 cancers. As of Jan. 3, 2025, updated topline results from the ongoing Phase 1 Duravelo-1 trial evaluating zelenectide pevedotin 5 mg/m^2 weekly plus pembrolizumab 200 mg once every three weeks in 22 first-line cisplatin-ineligible patients with mUC showed:

- 65% overall response rate (ORR) (13/20) among all efficacy-evaluable patients, and a 50% ORR (10/20) among patients with confirmed responses. Of the 3 unconfirmed responses, 1 patient remained on treatment at the time of the data cut.
- Median duration of response (mDOR) is not yet mature, with 12 patients still on treatment at the time of the data cut.
- Safety and tolerability profile continues to be broadly consistent with other Phase 1 zelenectide pevedotin monotherapy and combination cohorts. Adverse events of clinical interest such as peripheral neuropathy, skin reactions and eye disorders were primarily low grade. All cases of Grade 3 treatment-related adverse events (TRAEs) of clinical interest were reversible, and there were no Grade 4 or Grade 5 TRAEs of clinical interest. Notably, no patients withdrew from the study due to zelenectide TRAEs.

Altogether, these updated data continue to position zelenectide pevedotin as a potentially promising best-in-class therapy for mUC.

Bicycle Therapeutics is currently conducting the Phase 2/3 Duravelo-2 registrational trial evaluating zelenectide pevedotin plus pembrolizumab versus chemotherapy in first-line mUC (Cohort 1), and zelenectide pevedotin monotherapy and in combination with pembrolizumab in late-line mUC (Cohort 2). In each cohort, two doses of zelenectide pevedotin – 5 mg/m^2 weekly and 6 mg/m^2 two weeks on, one week off – are initially being assessed before a final dose is selected.

2024 Key Accomplishments

- Initiated the global Phase 2/3 Duravelo-2 trial for zelenectide pevedotin in mUC, providing multiple opportunities for potential accelerated approval.
- Presented updated monotherapy data for zelenectide pevedotin showing a promising 45% ORR in patients with late-line mUC who had not previously been treated with enfortumab vedotin. The data continue to support zelenectide pevedotin's emerging differentiated profile as a potential treatment for mUC.
- Presented updated monotherapy data for BT5528, a BTC® targeting EphA2, and BT7480, a Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®), in advanced solid tumors. The data support each molecule's emerging differentiated safety and tolerability profile and provide important information for continued dose selection exploration.
- Presented first human imaging data validating the potential of MT1-MMP as a novel target in the treatment of cancer and highlighting the potential of Bicycle® molecules for targeted radionuclide therapy. The company also selected EphA2 as its second radiopharmaceutical target.
- Reported monotherapy data for zelenectide pevedotin showing an enhanced response in late-line breast cancer and non-small cell lung cancer (NSCLC) patients with NECTIN4 gene amplification and/or polysomy. Based on these data, the U.S. Food and Drug Administration granted Fast Track designation to zelenectide pevedotin for the treatment of adult patients with previously treated, NECTIN4-amplified, advanced or metastatic triple-negative breast cancer and NSCLC.
- Raised $555 million to help advance research and development and strategic priorities. As of Sept. 30, 2024, the company had $890.9 million in cash and cash equivalents, with expected financial runway into 2H 2027.

2025 Strategic Priorities and Anticipated Milestones

Seek to transform treatment across multiple Nectin-4 associated cancers with zelenectide pevedotin

- Report additional Phase 1 Duravelo-1 combination data with pembrolizumab in first-line cisplatin-ineligible mUC in 2H 2025.
- Report longer-term follow-up Phase 1 Duravelo-1 monotherapy data in late-line mUC in 2H 2025.
- Report Phase 2/3 Duravelo-2 Cohort 1 and Cohort 2 dose selection data in 2H 2025.
- Initiate Phase 1 trials in NECTIN4 gene-amplified breast cancer (Duravelo-3) in 1H 2025 and NECTIN4 gene-amplified lung cancer (Duravelo-4) and multi-tumor (Duravelo-5) in 2H 2025.

Advance emerging Bicycle® Radionuclide Conjugates (BRC®) pipeline and progress strategy for leadership in next-generation radiopharmaceuticals

- Report additional MT1-MMP human imaging data in mid-2025.
- Report initial EphA2 human imaging data in 2H 2025.

Advance targeted therapeutics pipeline addressing novel targets that have historically been challenging to treat

- Report Phase 1 combination data for BT5528 plus nivolumab in 4Q 2025.
- Report Phase 1 combination data for BT7480 plus nivolumab in 4Q 2025.

J.P. Morgan Healthcare Conference Presentation and Webcast

Bicycle Therapeutics will highlight these updates and strategic priorities in a corporate presentation at the 43rd Annual J.P. Morgan Healthcare Conference on Tuesday, Jan. 14, 2025, at 5:15 p.m. PT, followed by a question-and-answer breakout session at 5:35 p.m. PT.

A live webcast of the presentation will be accessible from the Investor section of the company's website at www.bicycletherapeutics.com. A replay of the webcast will be archived and available following the event.

About Bicycle Therapeutics

Bicycle Therapeutics is a clinical-stage pharmaceutical company developing a novel class of medicines, referred to as Bicycle® molecules, for diseases that are underserved by existing therapeutics. Bicycle molecules 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 Bicycle molecules attractive candidates for drug development. The company is evaluating zelenectide pevedotin (formerly BT8009), a Bicycle® Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen; BT5528, a BTC molecule targeting EphA2, a historically undruggable target; and BT7480, a Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®) targeting Nectin-4 and agonizing CD137, in company-sponsored clinical trials. Additionally, the company is developing Bicycle® Radionuclide Conjugates (BRC®) for radiopharmaceutical use and, through various partnerships, is exploring the use of Bicycle® technology to develop therapies for diseases beyond oncology.

Bicycle Therapeutics is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Cambridge, Mass. For more information, visit www.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 Bicycle’s ability to continue its momentum, including with respect to the development of zelenectide pevedotin, BT5528 and BT7480 as well as potential radiopharmaceutical product candidates; the company’s plans to utilize a NECTIN4 gene amplification strategy in the clinical development of zelenectide pevedotin; Bicycle’s strategic goals to transform treatment across multiple Nectin-4 associated cancers, to become a leader in next-generation radiopharmaceuticals, and to advance a targeted therapeutics pipeline addressing novel targets that have historically been challenging to treat; the planned initiation of clinical trials of zelenectide pevedotin in breast cancer, lung cancer, and other cancers; achievement of multiple data milestones during the course of 2025, and the timing of announcement of data from clinical trials for zelenectide pevedotin, BT5528, BT7480, and human imaging data for MT1-MMP and EphA2 targeting Bicycle® Radionuclide Conjugates; expectations with respect to Bicycle’s financial runway; and the use of Bicycle’s technology through various partnerships to develop potential therapies in diseases beyond oncology. 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: uncertainties inherent in research and development and in the initiation, progress and completion of clinical trials and clinical development of Bicycle’s product candidates; the risk that Bicycle may not realize the intended benefits of its technology, partnerships or NECTIN4 gene amplification strategy; the risk that Bicycle may not achieve any of its clinical development strategies; timing of results from clinical trials; whether the outcomes of preclinical studies and prior clinical trials will be predictive of future clinical trial results; the risk that trials may have unsatisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; the risk that Bicycle’s projections regarding its expected cash runway are inaccurate or that its conduct of its business requires more cash than anticipated; 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 October 31, 2024, 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 otherwise required by law.

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