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

November 4, 2021
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.)

B900, Babraham Research Campus **Cambridge CB22 3AT** **United Kingdom**	**Not Applicable**
(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 2.02. Results of Operations and Financial Condition

On November 4, 2021, Bicycle Therapeutics plc (the "Company") issued a press release announcing financial results for the fiscal quarter ended September 30, 2021 and other business highlights. A copy of the press release is being furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information contained in Item 2.02 in this Current Report on Form 8-K (including Exhibit 99.1) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events

On November 4, 2021, the Company issued a press release announcing that the first patient has been dosed in its Phase I/II clinical trial of BT7480, a *Bicycle*® tumor-targeted immune cell agonist™, in patients with advanced solid tumors associated with Nectin-4 expression.

A copy of the press release is filed as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated into this Item 8.01 by reference.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Press Release issued November 4, 2021 regarding financial results and business highlights
99.2	Press Release issued November 4, 2021 regarding BT7480
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: November 4, 2021

Bicycle Therapeutics plc

By: /s/ Lee Kalowski

Name: Lee Kalowski
Title: Chief Financial Officer

Exhibit 99.1

Bicycle Therapeutics Reports Third Quarter 2021 Financial Results and Provides Corporate Update

- *Announced interim BT5528 Phase I clinical trial results and preliminary results from ongoing BT8009 Phase I clinical trial*
- *First Patient Dosed in Phase I/II Trial of Bicycle® Tumor-targeted Immune Cell Agonist™ BT7480 in Patients with Advanced Solid Tumors Associated with Nectin-4 Expression*
- *Cash was $259.5 million, which excludes $201.3 million in gross proceeds from Q4'21 public offering*
- *Genentech exercised an option in Q4'21 to initiate an additional program under the 2020 collaboration agreement*

CAMBRIDGE, England, & BOSTON, November 4, 2021 – 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 reported financial results for the third quarter ended September 30, 2021 and provided recent corporate updates.

"We recently provided a clinical update for our ongoing Phase 1 dose escalation trials in BT5528 and BT8009, the data from which support our conviction that the *Bicycle* platform offers a potentially differentiated approach to traditional targeted payload delivery," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "We were encouraged to see preliminary anti-tumor activity in both trials and across two tumor types, providing further insights as we continue to expand the application of our technology. We look forward to providing additional clinical data on BT5528 and BT8009 next year."

"Beyond our *Bicycle* Toxin Conjugates (BTC), we are also making progress across our other programs, including BT7480, our novel, fully synthetic *Bicycle* tumor-targeted immune cell agonist (*Bicycle* TICA™), which recently entered the clinic, as well as in our partnership with Genentech, which is now being expanded to include a new program under the collaboration. In addition, we recently entered into a collaboration agreement with Ionis Pharmaceuticals to develop targeted oligonucleotide therapeutics, which we believe further demonstrates the potential of the platform outside of oncology. Our plans to advance our programs and platform in oncology and beyond are supported by a strong balance sheet that has been further enhanced by the recent proceeds from an upsized public equity offering completed in October.

Third Quarter 2021 and Recent Highlights

- **Presented Interim BT5528 Phase I Clinical Trial Results at AACR-NCI-EORTC Conference.** In October 2021, Bicycle presented interim Phase I results for BT5528, a BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful. A total of 24 patients were dosed both prior to, and after, the implementation of the EphA2 immunohistochemistry (IHC) assay, with a median of seven prior lines of therapy. Among these patients, preliminary anti-tumor activity, including three partial responses, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, was observed in seven EphA2 positive urothelial and ovarian cancer patients. Based on the totality of the findings, Bicycle expects the recommended Phase 2 dose to be in the range of 6.5mg/m^2 to 8.5mg/m^2 every other week, a dose that Bicycle believes is within the therapeutic range based on both preclinical studies and preliminary clinical anti-tumor activity. Bicycle plans to initiate expansion cohorts in urothelial and ovarian cancers, as well as a basket cohort that includes head and neck, non-small cell lung, gastroesophageal and triple negative breast cancers in 2022.

- **Announced Preliminary Results from Ongoing BT8009 Phase I Clinical Trial.** In October 2021, Bicycle announced preliminary Phase I results for BT8009, a Nectin-4 targeting BTC with a potentially differentiated profile as compared to an FDA approved, Nectin-4 targeting antibody-drug conjugate. As of September 30, a total of 11 response evaluable urothelial cancer patients had been dosed in monotherapy cohorts, including four patients in the 2.5mg/m^2 dose cohort and seven in the 5.0mg/m^2 dose cohort. Among the four patients dosed at 2.5mg/m^2 weekly, three patients were observed to have at least stable disease, with a disease control rate of 75%, and one patient (25%) was observed to have a tumor reduction of 37%, meeting the criteria of a partial response under RECIST 1.1. Among the seven patients dosed at 5.0mg/m^2, five were observed to have at least stable disease, with a disease control rate of 71%, and three patients (43%) were observed to have tumor reductions meeting the criteria of a partial response under RECIST 1.1. The magnitude of tumor reductions ranged from 44% to 89%. In both cohorts, BT8009 has been tolerated, with no dose limiting toxicities observed to-date. Dose escalation remains ongoing, and patients are currently being enrolled in 7.5mg/m^2 weekly and every other week cohorts. A total of 14 clinical sites are active globally, including nine outside of the United States, and Bicycle expects to have up to 21 sites active this year.

- **Announced First Patient Dosed in Phase I/II Trial of *Bicycle*® Tumor-targeted Immune Cell Agonist™ BT7480 in Patients with Advanced Solid Tumors Associated with Nectin-4 Expression.** This is the Company's fourth product candidate to enter the clinic in as many years and is its first immuno-oncology asset to enter a clinical trial.

- **Raised Gross Proceeds of $201.3 Million in Public Offering.** In October 2021, Bicycle Therapeutics announced the closing of an upsized underwritten public offering which yielded gross proceeds of approximately $201.3 million. All of the ADSs in the offering were offered by Bicycle Therapeutics.

- **Genentech, a Member of the Roche Group, Has Exercised an Option to Initiate an Additional Program.** Genentech has expanded the exclusive strategic collaboration agreement with Bicycle to discover, develop and commercialize novel *Bicycle*-based immuno-oncology therapies. Bicycle and Genentech are collaborating on the discovery and pre-clinical development of novel *Bicycle*-based immunotherapies against multiple targets. Pursuant to the terms of the February 2020 agreement, Genentech has exercised an option to include a new program under the agreement, triggering a $10 million payment to Bicycle. None of the compounds in Bicycle's wholly owned oncology pipeline, including its immuno-oncology candidates, are included in the collaboration.

- **Bicycle Provides Update on BT1718, a First-Generation BTC Targeting Membrane Type 1-Matrix Metalloprotease (MT1-MMP), which is Currently Being Investigated in an Ongoing Phase IIa Portion of a Phase I/IIa Clinical Trial Sponsored and Funded by the Cancer Research UK Centre for Drug Development (CRUK).** Although there has been an acceleration in the second half of the year, enrollment in the Phase IIa trial has been slower than expected and remains below projections. Currently, five of the six planned clinical trial sites in the UK are open for enrollment, and CRUK may open up to two additional sites.

- **Announced Publication of Preclinical Data from BT7480 in the Journal for ImmunoTherapy of Cancer.** The article, titled "BT7480, a novel fully synthetic Bicycle tumor-targeted immune cell agonist™ (Bicycle TICA™) induces tumor localized CD137 agonism," outlines BT7480's potential to elicit rapid reprogramming of the tumor immune microenvironment, which was observed to lead to complete regressions and anti-tumor immunity with only intermittent drug exposure in syngeneic mouse tumor models.

- **Entered into an Exclusive License and Collaboration Agreement with Ionis Pharmaceuticals to Develop Targeted Oligonucleotide Therapeutics.** In July 2021, Ionis exercised its option under the terms of a December 2020 evaluation and option agreement and entered into an exclusive worldwide license and collaboration agreement for tissue-targeted delivery of oligonucleotide therapeutics using *Bicycles* with high affinity to the transferrin receptor (TfR1). Bicycle received $45 million upfront, which included a license fee, an option fee and an $11 million equity investment. Bicycle is also eligible to receive development, regulatory and commercial milestone payments and royalties for programs developed under the collaboration.

Financial Results

- Cash was $259.5 million as of September 30, 2021, compared to $136.0 million as of December 31, 2020. The increase in cash is primarily due to financing activities, including net proceeds of $102.6 million from Bicycle's at-the-market (ATM) offering program and net proceeds of $15.0 million from Bicycle's debt facility with Hercules Capital, as well as the $45.0 million received from Ionis under the 2021 collaboration agreement, offset by cash used for operating activities. Cash of $259.5 million at September 30, 2021 excludes the net proceeds from the public offering received in October 2021.

- Research and development expenses were $10.5 million for the three months ended September 30, 2021, compared to $7.4 million for the three months ended September 30, 2020. The increase in expense of $3.1 million for the three months ended September 30, 2021 as compared to the same period in the prior year was primarily due to direct program spend for BT8009 and other discovery and platform related expenses, as well as increased personnel related expenses, including $0.6 million of incremental non-cash share-based compensation expense.

- General and administrative expenses were $8.1 million for the three months ended September 30, 2021, compared to $7.2 million for the three months ended September 30, 2020. The increase of $0.9 million for the three months ended September 30, 2021 as compared to the same period in the prior year was primarily due to increased costs to support operations as a public company and increased personnel-related costs, including $0.6 million of incremental non-cash share-based compensation expense.

- Net loss was $14.7 million, or $(0.59) basic and diluted net loss per share, for the three months ended September 30, 2021, compared to net loss of $10.1 million, or $(0.52) basic and diluted net loss per share for three months ended September 30, 2020.

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, MA. 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 Bicycle’s anticipated advancement of its product candidates, including BT5528, BT8009 and BT7480; the advancement of Bicycle’s product candidate pipeline; the anticipated design of, initiation of, enrollment in and progression of Bicycle’s and its collaboration partners’ clinical trials; the availability and timing of data from clinical trials; the therapeutic potential of Bicycle’s product candidates; the development and potential commercialization of potential product candidates using Bicycle’s technology and under its license and collaboration agreements with Ionis and Genentech; the potential for Bicycle to receive milestone payments and royalties under its license and collaboration agreement with Ionis; potential site expansions in CRUK’s ongoing clinical trial of BT1718; the therapeutic potential for *Bicycles* in multiple applications; the potential of Bicycle’s platform to develop potential precision medicines; and Bicycle’s ability to achieve planned milestones. 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 and its collaboration partners’ abilities to meet other anticipated deadlines and milestones, presented by the ongoing COVID-19 pandemic; uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of Bicycle’s product candidates by Bicycle or its collaboration partners; the risk that Bicycle may not realize the intended benefits of its technology; availability and timing of results from preclinical studies and clinical trials; whether the outcomes of preclinical studies will be predictive of clinical trial results; 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; potential adverse effects arising from the testing or use of Bicycle’s product candidates; risks related to Bicycle’s ability to maintain existing collaborations and realize the benefits thereof; expectations for regulatory approvals to conduct trials or to market products; and other important factors, any of which could cause our 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 5, 2021, 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.

Bicycle Therapeutics plc
Condensed Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share data)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	**2020**	**2021**	**2020**
Collaboration revenues	$ 4,333	$ 3,842	$ 7,926	$ 6,542
Operating expenses:				
Research and development	10,513	7,363	31,924	23,091
General and administrative	8,114	7,154	23,596	18,351
Total operating expenses	18,627	14,517	55,520	41,442
Loss from operations	(14,294)	(10,675)	(47,594)	(34,900)
Other income (expense):				
Interest income	24	72	61	655
Interest expense	(823)	—	(2,164)	—
Total other income (expense), net	(799)	72	(2,103)	655
Net loss before income tax provision	(15,093)	(10,603)	(49,697)	(34,245)
Benefit from income taxes	(415)	(465)	(915)	(668)
Net loss	$ (14,678)	$ (10,138)	$ (48,782)	$ (33,577)
Net loss per share, basic and diluted	$ (0.59)	$ (0.52)	$ (2.06)	$ (1.81)
Weighted average ordinary shares outstanding, basic and diluted	25,039,990	19,426,833	23,719,124	18,504,013

Balance Sheets Data
(In thousands)
(Unaudited)

	September 30, 2021	December 31, 2020
Cash	$ 259,524	$ 135,990
Working capital	242,695	132,594
Total assets	281,333	161,152
Total shareholders' equity	170,823	95,460

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Exhibit 99.2

Bicycle Therapeutics Announces First Patient Dosed in Phase I/II Trial of *Bicycle*® Tumor-targeted Immune Cell Agonist™ BT7480 in Patients with Advanced Solid Tumors Associated with Nectin-4 Expression

- *BT7480 is the Company's Fourth Product Candidate to Enter the Clinic in the Past Four Years*

- *This is Bicycle's First Immuno-oncology Asset to Enter the Clinic*

CAMBRIDGE, England, & BOSTON, November 4, 2021 – 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 that the first patient has been dosed in the Phase I dose escalation portion of a company-sponsored Phase I/II trial of BT7480, a novel, fully synthetic *Bicycle* tumor-targeted immune cell agonist™ (*Bicycle* TICA™) targeting Nectin-4 and agonizing CD137. Preclinical studies have demonstrated that BT7480 activates CD137 only in the presence of Nectin-4 expressing tumor cells. The Phase I/II trial of BT7480 will be conducted in patients with advanced solid tumors associated with Nectin-4 expression.

"BT7480 is our first *Bicycle* TICA to enter the clinic and is one of a new class of tumor-targeting agents," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "Overexpression of Nectin-4, a well-validated tumor antigen, has been observed in several common tumor types and is associated with poor disease prognosis. Activation of CD137, a co-stimulatory receptor expressed on multiple components of the immune system, can drive anti-tumor immunity, but activation outside of the tumor may give rise to toxicity. Preclinical studies have shown encouraging results, and we look forward to studying the safety and efficacy of this unique asset as we begin the dose escalation portion of the trial."

The Phase I/II multi-center, open-label trial will evaluate BT7480 administered once weekly. Enrollment is ongoing in the Phase I dose escalation of BT7480 given as a monotherapy, and the Company plans to evaluate BT7480 dosed in combination with nivolumab in future Phase I dose escalation cohorts. The Phase I portion of the trial is primarily designed to assess the safety and tolerability of BT7480, and to determine a recommended Phase II dose (RP2D). Following selection of an RP2D, Bicycle expects to initiate a Phase II dose expansion portion with the primary objective of evaluating the clinical activity of BT7480 as monotherapy and in combination with nivolumab in patients with Nectin-4-positive tumors.

About Bicycle Therapeutics

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