Bicycle Therapeutics Announces First Patient Dosed in BT8009 Phase II Expansion Cohorts and Provides Program Update

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The Phase II multi-center, open label trial will evaluate BT8009 administered at the recommended Phase II doses of 5mg/m^2 and 7.5mg/m^2

Phase I dose escalation cohorts complete; results to be presented at a medical conference in 1H 2023

Confirmed RECIST response in a non-small cell lung cancer patient

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Nov. 8, 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 updates from the Phase I/II trial of BT8009 in patients with numerous cancer types where Nectin-4 is expressed. BT8009 is a potential first in class Bicycle Toxin Conjugate (BTC®) targeting Nectin-4, a protein located on the surface of cells that is highly expressed in urothelial cancer (UC) and other solid tumors.

“Dosing our first patient in the Phase II expansion portion of the BT8009 trial is a key development milestone for Bicycle,” said Kevin Lee, Ph.D., Chief Executive Officer. “Based on the data presented to date, we believe we are making an important step towards hopefully providing a clinically meaningful, differentiated therapy compared to what is currently available for UC as well as for other tumors that express Nectin-4, such as non-small cell lung cancer (NSCLC).”

“The results from the Phase I dose escalation portion of the BT8009 Phase I/II trial are very encouraging and we are excited to move rapidly forward with the dose expansion portion of the trial,” said Dominic Smethurst, MRCP, Chief Medical Officer of Bicycle Therapeutics. “BT8009 continues to exhibit potential best-in-class anti-tumor activity and a favorable tolerability profile, with a confirmed overall response rate from the latest cohorts consistent with previous findings from the trial, and we are pleased to see UC patients at the 5mg/m^2 dose remaining on therapy and continuing to respond. We are also pleased to report a confirmed partial response in an NSCLC patient and look forward to providing additional data from the Phase I escalation cohorts at a medical meeting in the first half of 2023.”

- **Phase I dose escalation portion of the Phase I/II trial is complete**. Two doses have been selected as the recommended Phase II doses (RP2Ds): 5mg/m^2 weekly and 7.5mg/m^2 2-weeks on, 1-week off (over a 21-day cycle). Updated results from the completed escalation portion of the trial include 49 patients and the company intends to present these results at a medical meeting in the first half of 2023.
- **In addition to clinical activity of BT8009 in UC as previously reported, confirmed clinical responses were observed in the 7.5mg/m^2 RP2D cohort as well as in the 10mg/m^2 every other week dose cohort.**
    - The confirmed Response Evaluation Criteria in Solid Tumors (RECIST) overall response rate in each of the 7.5mg/m^2 RP2D and 10mg/m^2 every-other-week cohorts was consistent with the findings observed and previously reported from the 5mg/m^2 weekly cohort.
    - At the 7.5mg/m^2 RP2D, confirmed RECIST responses were observed in UC and NSCLC patients. The overall median number of prior treatments was four. This dose was selected as a second RP2D based on its clinical activity and its alternative dosing schedule, which could provide improved convenience particularly in checkpoint inhibitor (CPI) combination settings.
- **All responding patients previously reported in the 5mg/m^2 weekly cohort remain on therapy.** The median duration of response has not yet been reached. As of the September 20, 2022 cutoff, all patients previously reported as having responses and on therapy have remained on therapy with ongoing responses.
- **Confirmed RECIST response in an NSCLC patient.** A confirmed partial response was observed in a 76-year-old patient with Nectin-4 positive metastatic adenocarcinoma. The patient entered the 7.5mg/m^2 RP2D cohort after four prior lines of therapy, including a CPI. As of the September 20, 2022 data cutoff, the patient remains on therapy after cycle seven with an ongoing response.
- **First patient dosed in Phase II expansion cohort.** The Phase II multi-center, open label trial will evaluate BT8009 administered at the RP2Ds of 5mg/m^2 and 7.5mg/m^2.
- **First-line metastatic UC in cisplatin ineligible patients in combination with a CPI is a priority for fast-to-market development.**
    - This is an indication with high unmet need as many patients have limited access to chemotherapy, often due to renal impairment.
    - The ongoing dose expansion includes cohorts evaluating the activity of BT8009 in CPI combination cohorts as well as in cohorts of patients with renal impairment.
    - Additionally, a Phase II study enrolling over 100 patients in combination with a CPI is being planned to start in

2023. The trial will include interim analyses that could be used to engage with regulatory authorities.

- **The company also intends to rapidly pursue multiple indications for BT8009, including in combination with a CPI. These include the following:**
  - Peri-operative muscle invasive UC in combination with a CPI
  - Second and third-line metastatic UC in patients who have been exposed to enfortumab vedotin as well as naïve patients as a monotherapy
  - Tumors outside of UC (NSCLC, triple negative breast cancer, and ovarian cancer) in combination with a CPI and as a monotherapy

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: the potential of BT8009 to target and kill cancer tumor cells; the initiation, progress, and timing of clinical trials of BT8009; and pursuit of additional indications for and further clinical development of this product candidate. Bicycle may not actually achieve the 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 intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: whether the outcomes of preclinical studies will be predictive of clinical trial results; the risk that trials and studies may be delayed and may not have satisfactory outcomes; 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 November 3, 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 otherwise required by law.

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