# Bicycle Therapeutics Announces Phase I Dose Escalation Results from Ongoing Phase I/II Study of BT8009

February 14, 2023

*50% overall response rate (ORR) and 75% clinical benefit rate, including one complete response in urothelial cancer at the 5 mg/m$^2$ dose on an intent-to-treat (ITT) basis*

*As of January 2023, median duration of response (mDOR) is estimated to be approximately 14 months among urothelial cancer patients in the 5 mg/m$^2$ cohort*

*Confirmed RECIST responses in non-small cell lung cancer (NSCLC) and breast cancer patients*

*Conference call scheduled for 8:00 a.m. ET*

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Feb. 14, 2023-- 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 monotherapy Phase I dose escalation results of the ongoing Phase I/II trial of BT8009, a novel BTC™ targeting Nectin-4. The results will be presented at the 2023 American Society for Clinical Oncology (ASCO) Genitourinary (GU) Cancers Symposium on Friday, February 17, 2023 in San Francisco, California. Today at 8:00 a.m. ET, the Company will host a conference call with BT8009 investigator Dr. Capucine Baldini and Dr. Daniel Petrylak to discuss the data being presented.

“We are encouraged by the Phase I dose escalation results as they continue to demonstrate the potential for BT8009 to be best-in-class for the treatment of urothelial cancer based on the observed anti-tumor activity and tolerability profile as well as the potential to treat other tumor types with significant unmet need,” said Kevin Lee, Ph.D., Chief Executive Officer. “Previously, we had reported a confirmed partial response in a non-small cell lung cancer patient and today we are pleased to announce a confirmed partial response in a breast cancer patient. Both of these patients are Nectin-4 positive. We are continuing to move forward with the dose expansion and Phase II portion of the clinical trial and look forward to providing an update by the end of 2023.”

“These data reaffirm the possibility for BT8009 to become a significant new treatment option for patients,” said Capucine Baldini, M.D., Medical Oncologist, Gustave Roussy. “The anti-tumor activity observed to date in heavily pre-treated urothelial, lung and breast cancer patients shows that BT8009’s Nectin-4-targeting properties make it a potentially differentiated treatment option compared to other available treatments.”

“BT8009 has the potential to become an important player in the treatment landscape for urothelial cancer and other solid tumors,” said Daniel Petrylak, M.D., Professor of Medicine and Urology, Yale University. “Clinicians need differentiated treatments for patients that can offer lower rates of rash and neuropathy thus leading to longer durations of treatment. Given the preliminary tolerability and response pattern with BT8009 in this Phase I dose escalation, it justifies exploring BT8009 both as a monotherapy and in combination in the ongoing expansion cohorts.”

**BT8009, a BTC targeting Nectin-4, has demonstrated anti-tumor activity in heavily pre-treated urothelial, lung and breast cancer patients with signs of differentiation compared to antibody-based approaches.** Bicycle established two recommended Phase II doses (RP2Ds) at 5 mg/m$^2$ weekly and 7.5 mg/m$^2$ 2 weeks on, 1-week off (over a 21-day cycle). The company is currently focusing its efforts on the 5 mg/m$^2$ weekly dose and enrollment in the expansion cohorts remains ongoing.

- **Preliminary signs of anti-tumor activity observed.** As of the September 20, 2022 data cut off, 49 patients were dosed in the Phase I escalation portion of the ongoing Phase I/II trial with a median of three prior lines of therapy.
  - A total of 24 urothelial cancer patients were dosed. Of these, eight patients were dosed at the RP2D of 5 mg/m$^2$ weekly.
    - Among these eight patients, one patient had a complete response (13%), and three patients had a partial response (38%) under the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, resulting in an ITT ORR of 50%. Two additional patients had stable disease for over 16 weeks, resulting in a clinical benefit rate (CBR) of 75%. The remaining two patients in the cohort consisted of one stable disease and one non-evaluable patient.
    - Of the eight urothelial patients dosed at 5 mg/m$^2$ weekly, seven were response evaluable. Amongst these seven patients, all (100%) were observed to have at least some degree of tumor shrinkage, including the four with a RECIST version 1.1 response (57% ORR on a response-evaluable basis).
    - As of January 2023, mDOR is estimated to be approximately 14 months. Two out of four responders in this cohort remain on therapy with ongoing responses.
  - **Response rates in urothelial patients in the 7.5 mg/m$^2$ 2 weeks on, 1-week off (over a 21-day cycle) and 10 mg/m$^2$ every other week cohort were consistent with that of the 5 mg/m$^2$ weekly cohort on an ITT basis.** One of two patients in the 7.5 mg/m$^2$ 2 weeks on, 1-week off (over a 21-day cycle) cohort had a partial response and two of four patients in the 10 mg/m$^2$ every other week cohort had a partial response, for an ORR of 50% in

each of these cohorts. Both of these cohorts deliver the same amount of MMAE payload as the 5 mg/m$^2$ weekly dose over a six-week period.
    - **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 7.5 mg/m$^2$ 2 weeks on, 1-week off (over a 21-day cycle) cohort after four prior lines of therapy, including a checkpoint inhibitor. As of the September 20, 2022 data cutoff, the patient remains on therapy with an ongoing response.
    - **Confirmed RECIST response in a breast cancer patient.** A confirmed partial response was observed in a 79-year-old patient with Nectin-4 positive metastatic adenocarcinoma. The patient entered the 10 mg/m$^2$ every other week cohort after one prior line of therapy. As of December 2022, the patient remains on therapy with an ongoing response.

- **BT8009 was well tolerated across all 49 patients in the study, with a low incidence of adverse events common to antibody-based approaches.** The most common treatment-related adverse events across the study were gastroenterologically related and fatigue. Across all patients at all doses, there was a low incidence of skin rash of any form, eye disorders, neuropathy of any form and no cases of pneumonitis in any patient at any dose. The most common Grade 3 or higher treatment-related adverse event was neutropenia: seven cases or 14%; four of these were at doses above the RP2Ds. There were three subjects with serious adverse events (SAEs) at or above Grade 3 that were drug related (6%). Of these, none was in the 5 mg/m$^2$ cohort. Median percentage relative dose intensity was 99%, reflecting a low level of dose modifications especially for a Phase I dose escalation trial in a heavily pre-treated population.
- **BT8009 well tolerated at or below the two RP2Ds**. At or below the RP2Ds of 5 mg/m$^2$ weekly and 7.5 mg/m$^2$ 2 weeks on, 1-week off (over a 21-day cycle), treatment-related dose modifications were rare. There were no treatment-related discontinuations. The incidence of Grade 3 or higher related adverse events at or below the two RP2Ds was low. At the 5 mg/m$^2$ weekly dose, there were no cases of Grade 3 or higher skin rash, eye disorders, neuropathy or pneumonitis.

**Bicycle advancing BT8009 in ongoing expansion cohorts**. In November 2022, Bicycle announced the dosing of the first patient in the part B dose expansion portion of the Phase I/II trial. Up to 66 patients will be enrolled in the initial monotherapy expansion cohorts, with the ability to further expand enrollment based on results from these cohorts. These monotherapy cohorts include urothelial cancer patients who are enfortumab vedotin (EV) naïve and those who are EV exposed, as well as cohorts in ovarian, triple negative breast and non-small cell lung cancers. A Phase II trial of BT8009 in combination with pembrolizumab remains on track to commence this year.

**Poster Presentation Details**

**Title:** BT8009-100: A Phase I/II Study of a Novel Bicyclic Peptide and MMAE Conjugate BT8009 in Patients with Advanced Malignancies Associated with Nectin-4 Expression, Including Urothelial Cancer
**Abstract #:** 498
**Presenter:** Capucine Baldini, M.D., on behalf of the BT8009-100 investigators
**Session Title:** Poster Session B: Prostate Cancer and Urothelial Carcinoma
**Date/Time:** Friday, February 17, 3:30 p.m. to 5:00 p.m.; 8:15 p.m. to 9:15 p.m. ET

**Conference Call Details**

Bicycle Therapeutics will host a conference call and webcast today, February 14, 2023 at 8:00 a.m. ET to review the data being presented. To access the call, please dial (866) 652-5200 (domestic) or (412) 317-6060 (international) and provide the Conference ID 10174689. 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, 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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**Investors:**
David Borah, CFA
SVP, Capital Markets & Corporate Communications
david.borah@bicycletx.com
617-203-8300

**Media:**
Argot Partners
Sarah Sutton
bicycle@argotpartners.com
212-600-1902

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