Bicycle Therapeutics Announces Interim BT5528 Phase I Clinical Trial Results and Preliminary Results from Ongoing BT8009 Phase I Clinical Trial

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- BT5528 Phase I anti-tumor activity observed in late line patients, with 2 partial responses out of 2 urothelial cancer patients dosed and an 80% disease control rate in 5 EphA2-positive ovarian cancer patients, including 1 partial response

- A recommended BT5528 Phase II dose (RP2D) range has been established at 6.5-8.5mg/m^2 every other week; expansion cohorts expected to initiate in 2022

- In the ongoing BT8009 Phase I trial in monotherapy cohorts, 4 out of 11 urothelial patients had partial responses; Phase I dose escalation remains ongoing, with no dose limiting toxicities (DLTs) yet observed

- BT5528 data to be presented at a virtual plenary session today at 1:25pm ET at the AACR-NCI-EORTC meeting; conference call scheduled for 3:00pm ET

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Oct. 7, 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 provided a clinical update of its wholly-owned, next-generation *Bicycle* Toxin Conjugates (BTCs), reporting interim Phase I trial results for BT5528 and preliminary findings from the ongoing dose escalation portion of the BT8009 clinical trial.

"We are pleased to provide a clinical update for two of our wholly-owned BTCs currently undergoing Phase 1 dose escalation trials in late line cancer patients," said Dominic Smethurst, MA, MBChB, MRCP, MFPM, Chief Medical Officer of Bicycle Therapeutics. "We are delighted to see preliminary anti-tumor activity in both trials and across two tumor types, as well as to report tolerability profiles that may demonstrate differentiation from antibody-based approaches."

"These data support our belief that the Bicycle platform offers a potentially differentiated approach to traditional toxin delivery. The data generated from these molecules provide a wealth of information and insights as we continue to expand the application of our technology and generate additional *Bicycle*- targeted therapeutics with the intention of making a meaningful difference to cancer patients," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "We look forward to providing additional clinical data on BT5528 and BT8009 next year, and initiating our Phase I/II study for BT7480 later this year."

BT5528, a BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful, has demonstrated preliminary anti-tumor activity. Bicycle has established an RP2D range and is pursuing enrollment in expansion cohorts

- **Preliminary signs of anti-tumor activity observed.** 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. Amongst these patients, preliminary anti-tumor activity was observed in urothelial and ovarian cancer patients.
    - A total of two BT5528 monotherapy urothelial patients were dosed. Both (100%) were observed to have tumor reductions constituting a partial response under Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The administered doses in these patients ranged from 6.5mg/m^2 to 10 mg/m^2 every other week.
    - A total of eight BT5528 monotherapy ovarian cancer patients were dosed. Of these eight, five were determined to be EphA2-positive based on the IHC assay. Anti-tumor activity was observed in four of the five (80%) patients, including one (20%) that constituted a partial response under RECIST version 1.1 criteria. The range of administered doses in these patients was 6.5- 8.5mg/m^2 every other week.
- **Doses of BT5528 administered to date have been tolerated in the ongoing Phase I portion of the Phase I/II trial.** In addition, and in contrast to the toxicities observed with MedImmune's EphA2 antibody-drug conjugate (ADC) MEDI-547, Bicycle has observed no signs of coagulopathy to date.
- **Based on the Phase I results, Bicycle has established an RP2D range.** BT5528 has been dosed up to 8.5mg/m^2 every week and 10mg/m^2 every other week. Some mild and transient neutropenia was observed at 8.5mg/m^2 every week, although this did not constitute a DLT. At 10mg/m^2 every other week, two DLTs were observed (Grade 3 fatigue and Grade 3 pneumonitis). The most common Grade 3 and above events were neutropenia, anemia and pneumonitis and there were two Grade 5 events: tumor lysis syndrome and renal failure caused by GI-related dehydration. Based on the totality of the findings, the RP2D is expected to be in the range of 6.5 mg/m^2 to 8.5mg/m^2 every other week, a dose that is believed to be within the therapeutic range based on both preclinical studies and preliminary clinical anti-tumor activity.

- **Bicycle to advance BT5528 in expansion cohorts.** Based on the findings from the Phase I trial, Bicycle plans to initiate expansion cohorts in urothelial and ovarian cancers as well as a basket that includes head and neck, non-small cell lung, gastroesophageal and triple negative breast cancers in 2022. The trial will enroll up to 56 patients in the initial expansion cohorts, with the ability to further expand enrollment based on the results of the initial expansion cohorts.

BT8009, a Nectin-4 targeting BTC with a potentially differentiated profile as compared to a Nectin-4 targeting ADC has shown preliminary anti-tumor activity in the ongoing Phase I portion of its Phase I/II trial.

- **Preliminary signs of anti-tumor activity in urothelial patients observed.** As of September 30, a total of 11 response evaluable urothelial cancer patients have been dosed in monotherapy cohorts of 2.5mg/m^2 and 5.0mg/m^2 weekly in the ongoing trial. Of these, four patients were in the 2.5mg/m^2 dose cohort and seven in the 5.0mg/m^2 dose cohort. Prior to enrollment, all patients had previously received at least two prior lines of therapy, with a median of two and a range of two-to-six prior therapies. A total of four patients (36%) were observed to have tumor reductions that constituted partial responses under RECIST 1.1, with a range in tumor reductions from 37% to 89% among these patients.

    - Four response evaluable patients were dosed at 2.5mg/m^2 weekly. Among these four patients, 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.

    - Seven response evaluable patients were dosed at 5.0mg/m^2 weekly. Among these seven patients, 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%.

- **Dose escalation remains ongoing.** At both 2.5mg/m^2 weekly and 5.0mg/m^2 weekly, BT8009 has been tolerated, with no DLTs observed to-date. At 5.0mg/m^2 weekly, BT8009 is estimated to administer over 35% more MMAE per four-week dosing cycle compared to the antibody-based drug conjugate, enfortumab vedotin. The escalation remains ongoing, and patients are currently being enrolled in 7.5mg/m^2 weekly and every other week cohorts.

- **BT8009 enrollment ongoing.** A total of 14 clinical sites are active globally, including nine outside of the United States. Bicycle expects to have up to 21 sites active this year.

Conference Call Details

Bicycle Therapeutics will host a conference call and webcast on Thursday, October 7 at 3:00 p.m. ET to review the BT5528 trial data being presented at the AACR-NCI-EORTC meeting and provide an update on preliminary findings from the BT8009 trial. To access the call, please dial (800) 377-9118 (domestic) or (409) 937-8920 (international) and provide the Conference ID 2287246. 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, and BT8009, a second-generation BTC™ targeting Nectin-4, a well-validated tumor antigen, 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 Centre for Drug Development of Cancer Research UK. 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; anticipated design of, initiation of, enrollment in and progression of Bicycle’s clinical trials; the availability of data from clinical trials; and the therapeutic potential of Bicycle’s 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 initiation 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; availability and timing of results from 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 may be delayed and may not have satisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; 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.

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