Bicycle Therapeutics Announces Pipeline Progress Update

January 14, 2021

- BT1718 progressing in Cancer Research UK sponsored Phase IIa clinical trial

- Phase I trial of BT5528 currently dosing within predicted therapeutic range; preliminary signs of anti-tumor activity observed, including a partial response

- BT8009 pharmacokinetic profile consistent with preclinical predictions based on early clinical data; first clinical site outside the United States expected to open for recruitment this quarter

- BT7480 on track for Phase I trial start in 2H '21; early immuno-oncology discovery has resulted in new programs targeting natural killer cells, which are now moving into lead optimization

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Jan. 14, 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 progress updates for its wholly owned, next-generation *Bicycle* Toxin Conjugates (BTCs) targeting oncological indications, as well as its novel, fully synthetic *Bicycle* tumor-targeted immune cell agonists (TICAs™).

"We are excited to start 2021 by announcing clinical progress across our internal oncology pipeline, with both our next-generation *Bicycle* Toxin Conjugates (BTCs) and our *Bicycle* tumor-targeted immune cell agonists (TICAs), positioning us for multiple inflection points over the coming year," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "Our lead program, BT1718, remains on track in the Cancer Research UK sponsored Phase IIa trial, and notably, we have observed preliminary signs of anti-tumor activity in the Phase I monotherapy portion of our trial of BT5528, including one partial response and additional evidence of tumor reductions. We continue to make strong progress with BT8009 as we expect to begin recruiting at our first clinical site outside of the US shortly, and we are encouraged by its initial pharmacokinetic (PK) profile. In our immuno-oncology pipeline, we expect BT7480, for which preclinical data has indicated a potential unique anti-tumor killing mechanism, to enter the clinic this year, and we have identified new TICAs targeting natural killer (NK) cells, which we are moving into lead optimization. Overall, we are pleased with our progress as we pursue our goal of realizing the full potential of our disruptive *Bicycle* technology, and we look forward to providing additional updates on our oncology pipeline, as well as our partnered programs beyond oncology, throughout the year."

BT1718, a potential first-in-class BTC targeting a key tumor antigen MT1-MMP, is progressing in the Phase IIa portion of the Cancer Research UK sponsored Phase I/IIa clinical trial in patients with advanced solid tumors

- **Patient enrollment in the Phase IIa portion of the Phase I/IIa trial sponsored by Cancer Research UK's Center for Drug Development remains ongoing and is proceeding according to schedule.** In this Phase IIa portion of the trial, all patients are MT1-MMP-positive based on a prespecified tumor membrane H-score**.** To date, the percentage of patients determined to be MT1-MMP-positive at the pre-specified cutoff is consistent with previous translational research findings. Enrollment is ongoing at four clinical sites, with additional sites expected to begin enrolling patients during the first half of 2021. Patients are currently being enrolled into two solid tumor cohorts, one in squamous non-small cell lung cancer (NSCLC) and the other in an all-comers "basket" cohort. Depending on results from these first two cohorts, Cancer Research UK may initiate up to two additional cohorts.

- **In the Phase I portion of the Phase I/IIa trial, BT1718 was generally well-tolerated.** As previously announced, based on the Phase I trial results, 20 mg/m^2 of BT1718 administered once weekly was selected as the Phase IIa dose. This dose is within the efficacious dose range predicted by preclinical models, in which an equivalent dose level was associated with complete responses. With once-weekly dosing, BT1718 appeared tolerable, with manageable adverse events. Though the primary objective of the Phase I portion of the BT1718 trial was evaluating safety and tolerability in an unselected group of patients with advanced solid tumors, some signs of anti-tumor activity were observed:

    - At doses of between 9.6 mg/m^2 and 32.0 mg/m^2 administered once-weekly, 13 out of 24 response evaluable patients at the eight week timepoint exhibited best response of at least stable disease. Ten of these 13 patients had a greater than 10% reduction in at least one target lesion, including a tumor reduction of 68% observed in one patient, a reduction that meets the RECIST Version 1.1 criteria of a partial response.

BT5528, a BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful, is currently being administered at doses within the predicted therapeutic range, with preliminary signs of anti-tumor activity

- **Doses of BT5528 administered to date appear well-tolerated in the ongoing Phase I portion of the Phase I/II trial.** BT5528 has been tolerated up to 8.5mg/m^2 weekly, which Bicycle believes, based on pre-clinical studies, is toward the top

of the therapeutic range, with transient neutropenia observed at that dose. Dose finding for the Phase II portion of the trial remains ongoing and additional weekly and every other week doses are currently being explored. Currently administered doses are in the predicted therapeutic range, delivering over 15-fold more toxin than MedImmune's EphA2 antibody-drug conjugate (ADC) MEDI-547. In addition, and in contrast to the toxicities observed with MEDI-547, no signs of coagulopathy have been observed to date.

- **Clinical PK profile of BT5528 is consistent with preclinical predictions.** Early data received from tumor biopsies reveal that 24 hours after infusion of BT5528, tumor levels of the MMAE cytotoxin payload are approximately 10-fold greater than the corresponding plasma levels. Emerging, qualitative metabolite identification data from the clinical trial supports the hypothesis that BTCs undergo reduced hepatic metabolism and are eliminated renally.

- **Preliminary signs of anti-tumor activity have been observed.** Although dosing continues to be refined, Bicycle has observed preliminary findings consistent with anti-tumor activity. An EphA2 immunohistochemistry (IHC) assay was deployed during 2020, enabling pre-selection of patients in the Phase I portion of the trial. Since implementation of the IHC assay, patients are prospectively screened and are eligible for enrollment based on a prespecified H-score. To date, two EphA2 selected patients have enrolled in the trial, one of whom was response evaluable.

    - In the response evaluable prospectively screened EphA2 positive patient, a urothelial patient currently receiving 6.5mg/m^2 of BT5528 every other week, whose prior lines of therapies included both a PD-1 inhibitor and enfortumab vedotin, a 43% reduction in target lesions was observed at the first radiologic response assessment, constituting a partial response under RECIST version 1.1 criteria. Reductions in non-target lesions were also observed, and the patient remains enrolled in the trial.

    - In addition, an ovarian cancer patient, enrolled prior to implementation of the EphA2 assay, currently receiving 4.4mg/m^2 of BT5528 every week, who had been previously treated with chemotherapy, a vascular endothelial growth factor (VEGF) inhibitor and a poly ADP ribose polymerase (PARP) inhibitor, has achieved an ongoing 25% reduction in target lesions, constituting stable disease. The patient, first dosed in May 2020, has completed eight cycles of BT5528 and remains enrolled in the trial. Subsequently the patient was retrospectively analyzed for EphA2 status and determined to be positive, but below the current enrollment H-score cutoff.

- **Enrollment in the Phase I/II trial of BT5528 remains on track and additional sites are expected to begin enrolling patients in 2021.** Enrollment continues to track to plan, with five clinical sites currently active, including four in the United States and one now recruiting patients in the United Kingdom. Bicycle expects that up to five additional sites will be opened in the first half of this year, primarily in the United Kingdom and Europe. A planned total of up to 17 worldwide sites is expected to be active in 2021, with sites prioritizing the enrollment of eligible EphA2-positive patients in the monotherapy cohorts.

BT8009, a Nectin-4 targeting BTC with a potentially differentiated profile as compared to a Nectin-4 targeting antibody-drug conjugate (ADC) is progressing in the Phase I/II trial, with the first clinical site outside of the United States expected to open for patient recruitment this quarter

- **BT8009 is advancing in the Phase I portion of the Phase I/II clinical trial.** Early clinical data supports a PK profile that is consistent with both preclinical predictions and data to date from Bicycle's ongoing Phase I trial of BT5528, which utilizes the same linker and toxin payload.

- **Enrollment in the Phase I/II trial of BT8009 remains on schedule.** As planned, sites in the United States opened first, with two sites initially recruiting patients. The first clinical site outside of the United States is expected to open for patient recruitment this quarter. During the first half of 2021, Bicycle expects up to nine additional sites to open, primarily in Canada and the United Kingdom, with further geographic expansion during the year. In total, Bicycle expects up to 21 clinical sites to be open, with prioritization given to enrolling appropriate Nectin-4-positive patients in the monotherapy cohorts.

Further clinical updates for all three BTC programs - BT1718, BT5528, and BT8009 – are expected during 2021

Novel, fully synthetic TICAs continue to advance, with BT7480 expected to enter the clinic this year and new TICA programs targeting natural killer (NK) cells identified and moving into lead optimization

- **IND preparation for BT7480, a novel TICA, remains on track, for a potential clinical start during the second half of 2021.** BT7480 is a fully synthetic TICA that contains *Bicycles* targeting Nectin-4 and the key immune cell receptor CD137. BT7480 has been shown in preclinical models to rapidly penetrate tumors, have anti-tumor activity, and induce immune memory specific to the implanted tumor. IND-enabling activities for BT7480 are ongoing and the Phase I clinical trial is on track to commence in the second half of the year.

- **Early immuno-oncology (I-O) discovery efforts have resulted in the identification of TICA candidates targeting NK cells.** Bicycle Therapeutics is moving these programs into lead optimization and will focus its early I-O development efforts in 2021 on advancing these novel *Bicycles*.

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's lead product candidate, BT1718, a *Bicycle* Toxin Conjugate (BTC) that targets MT1-MMP, is being investigated in an ongoing Phase I/IIa clinical trial in collaboration with the Centre for Drug Development of Cancer Research UK. Bicycle is also evaluating BT5528, a second-generation BTC targeting EphA2, in a company-sponsored Phase I/II trial. BT8009 is a BTC targeting Nectin-4, a well-validated tumor antigen, and is also currently being evaluated a Company-sponsored Phase I/II trial. 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.

About Cancer Research UK's Centre for Drug Development

Cancer Research UK has an impressive record of developing novel treatments for cancer. The Cancer Research UK Centre for Drug Development has been pioneering the development of new cancer treatments for more than 25 years, taking over 160 potential new anti-cancer agents into clinical trials in patients. It currently has a portfolio of around 20 new anti-cancer agents in preclinical development, Phase I or early Phase II clinical trials. Six of these new agents have made it to market including temozolomide for brain cancer, abiraterone for prostate cancer and rucaparib for ovarian cancer. Two other drugs are in late development Phase III trials.

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 anticipated advancement of preclinical development efforts and initiation and progression of clinical trials; anticipated enrollment in and progression of Bicycle's and its collaborators' clinical trials; the availability of data from clinical trials and preclinical studies; anticipated regulatory filings; the therapeutic potential of Bicycle's product candidates; 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 our Annual Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 5, 2020, 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 as a result of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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