Bicycle Therapeutics Announces Presentation of Updated Data from Phase I/IIa Trial Evaluating BT1718 in Patients with Advanced Solid Tumors at ESMO 2019 Annual Congress

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- Phase I dose escalation continues; dosing is within the therapeutic range predicted by preclinical models

- Early analysis of data shows stable disease in 54% of evaluable patients at eight weeks, across all cohorts of the all-comers Phase I escalation

- Tumor biopsies indicate targeted delivery of DM1 toxin to tumor consistent with preclinical models

LONDON & CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Sep. 28, 2019-- Bicycle Therapeutics plc (NASDAQ: BCYC), a biotechnology company pioneering a new class of therapeutics based on its proprietary bicyclic peptide (*Bicycles*®) product platform, today announced the presentation of updated data from a Phase I/IIa trial conducted in collaboration with Cancer Research UK and evaluating BT1718 in an unselected group of patients with advanced solid tumors. The results are being presented by Natalie Cook, Ph.D., a study investigator and Senior Clinical Lecturer at the University of Manchester, today from 12:00-13:00 CET in a poster session at the European Society of Medical Oncology (ESMO) 2019 Annual Congress in Barcelona, Spain. The poster is available on the Publications section of bicycletherapeutics.com.

“The data being presented at ESMO demonstrate encouraging progress of the dose escalation portion of the Phase I/IIa trial evaluating BT1718,” said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. “We believe these early data underscore the potential of *Bicycle*s as a novel therapeutic modality and plan to provide additional updates from across our pipeline at medical meetings through the rest of this year.”

Patients in the Phase I dose escalation were assessed for anti-tumor activity, safety and pharmacokinetics up to the data cutoff of August 7, 2019. Based on data from patients in cohorts across dose levels tested, many of which are below the predicted therapeutic range, 13 of 24 evaluable patients (54%) had stable disease at the eight-week timepoint, including a patient who experienced a 45% reduction in a target lesion. With once-weekly dosing, which is the expected schedule for the Phase IIa portion of the study, BT1718 has appeared tolerable, with manageable adverse events. The Phase I once-weekly dose escalation portion of the trial is ongoing, with dosing at levels equivalent to those associated with preclinical responses.

Across all dose levels and schedules tested, the most common treatment-related adverse events (>15%, n=28) were anemia, diarrhea, nausea, vomiting, fatigue, alanine aminotransferase increase, aspartate aminotransferase increase, blood alkaline phosphatase increase, gamma-glutamyltransferase increase, decreased appetite, lethargy and peripheral neuropathy.

Evaluation of pharmacokinetics demonstrated that BT1718 area under the curve (AUC) was approximately dose proportional over the range 0.6-25 mg/m^2, and cycle 2 values were consistent with cycle 1. Mean (±SD) plasma clearance (CLp) was 33.6 (±24.5) L/h, with mean (±SD) volume of distribution (Vss) of 12.5 (±7.3) L, resulting in a terminal half-life ($t_{1/2}$) of 0.2 to 0.5 hours. Two tumor biopsies were obtained from patients dosed at levels above 15 mg/m^2 and analysis showed delivery of DM1 to the tumor consistent with preclinical models. These findings suggest rapid tumor penetration by BT1718. Further plasma and tumor DM1 analysis is ongoing to assess the extent of DM1 retention.

“We are on track to achieve the primary objectives of the Phase I portion of the study,” said Udai Banerji, M.D., Ph.D, chief investigator of the study and Deputy Director of the Drug Development Unit at The Institute of Cancer Research, London and The Royal Marsden NHS Foundation Trust. “BT1718 represents an exciting potential first-in-class drug, which appears tolerable in Phase I evaluation. Importantly, in two patient biopsies, we observed presence of cytotoxic payload to tumors consistent with targeted delivery and in a manner predicted by our preclinical models.”

Nigel Blackburn, Ph.D., Cancer Research UK's Director of Drug Development, said: “Based on our experience, these early clinical data are very promising and a testament to our strong partnership with Bicycle Therapeutics. We are pleased to help accelerate potentially groundbreaking new therapeutics such as BT1718 into clinical trials. This is an excellent example of the innovative work our Centre of Drug Development can support and is an important step toward helping more people survive cancer."

The Phase I/IIa study of BT1718 is being sponsored by Cancer Research UK. The primary objectives of the Phase I dose escalation portion of the trial are to select the recommended Phase II dose (RP2D) by establishing the maximum tolerated dose and maximum administered dose, and to assess the safety and toxicity profile of BT1718 in patients with advanced solid tumors. Following selection of the once-weekly RP2D, the Phase IIa portion of the study, consisting of up to four cohorts in selected indications in which MT1-MMP is expressed, will be initiated.

About BT1718

BT1718 is a *Bicycle* Toxin Conjugate being developed by Bicycle Therapeutics that targets Membrane Type 1 Matrix Metalloproteinase (MT1-MMP), also known as MMP-14, which has an established role in cell invasion and metastasis, is linked to poor outcomes and is over-expressed in many solid tumors. BT1718 has demonstrated promising target-dependent efficacy in preclinical models, including both cell- and patient-derived xenografts that are resistant to treatment with standards of care. In addition, it shows only a subset of the toxicities typically associated with other highly potent cancer treatments.

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, is a *Bicycle* Toxin Conjugate being investigated in an ongoing Phase I/IIa clinical trial in collaboration with 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.

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, formerly the Drug Development Office, has been pioneering the development of new cancer treatments for 25 years, taking over 140 potential new anti-cancer agents into clinical trials in patients. It currently has a portfolio of around 30 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. This rate of success is comparable to that of any pharmaceutical company.

About Cancer Research UK

- Cancer Research UK is the world's leading cancer charity dedicated to saving lives through research.
- Cancer Research UK's pioneering work into the prevention, diagnosis and treatment of cancer has helped save millions of lives.
- Cancer Research UK receives no funding from the UK government for its life-saving research. Every step it makes towards beating cancer relies on vital donations from the public.
- Cancer Research UK has been at the heart of the progress that has already seen survival in the UK double in the last 40 years.
- Today, 2 in 4 people survive their cancer for at least 10 years. Cancer Research UK's ambition is to accelerate progress so that by 2034, 3 in 4 people will survive their cancer for at least 10 years.
- Cancer Research UK supports research into all aspects of cancer through the work of over 4,000 scientists, doctors and nurses.

For further information about Cancer Research UK's work or to find out how to support the charity, please call 0300 123 1022 or visit www.cancerresearchuk.org. Follow us on Twitter and Facebook.

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 clinical development of BT1718 or any of Bicycle's other product candidates or programs, including the timing and receipt of results from the Phase I/IIa clinical trial of BT1718, the progression of this clinical trial into Phase IIa, and the expected dosing schedule in this clinical trial. 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: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of Bicycle's product candidates; availability and timing of results from preclinical studies and clinical trials; whether 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 BT1718 or other 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 product; and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, as described in greater detail in the section entitled "Risk Factors" in the final prospectus for our initial public offering, filed with the Securities and Exchange Commission (SEC) on May 23, 2019, 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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