Bicycle Therapeutics Announces Publication of BT5528 Mechanism of Action in AACR Journal Molecular Cancer Therapeutics

May 12, 2020

- BT5528 optimized to have distinct physiochemical and in vivo *properties thought to enable more favorable preclinical safety, efficacy profiles than those of an antibody drug conjugate*

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--May 12, 2020-- 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 that a research paper describing the mechanism of action for the Company's first second-generation *Bicycle* Toxin Conjugate (BTC), BT5528, has been published in the American Association for Cancer Research (AACR) journal *Molecular Cancer Therapeutics.* The manuscript, titled "MMAE delivery using the *Bicycle* toxin conjugate BT5528," discusses the preclinical profile of BT5528, which has physiochemical properties thought to enable more favorable safety and efficacy profiles than antibody drug conjugates (ADCs) with the same tumor antigen target and similar cytotoxic payload. The e-publication can be found here.

"*Bicycles* are a unique therapeutic modality designed to address clinical needs that can't be met by biologic or small molecule approaches," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "The preclinical data for BT5528 published in *Molecular Cancer Therapeutics* suggest that the key features of *Bicycles,* such as their low molecular weight, short systemic half-life and renal route of elimination, can result in a therapeutic candidate with an *in vivo* pharmacokinetic profile that yields a wider preclinical therapeutic index than that of a comparator ADC."

BT5528 is a second-generation BTC, which uses a valine-citrulline cleavable linker and a cytotoxin MMAE payload, that targets EphA2, a tumor antigen that is overexpressed in a wide range of solid tumor types and is associated with poor outcomes, making it ideal for selective payload targeting using ADCs and other approaches. The manuscript published in *Molecular Cancer Therapeutics* describes the preclinical development of BT5528, which involved a suite of pharmacokinetic, efficacy and safety studies aimed at derisking the toxicology that limited development of MedImmune's MEDI-547, an ADC comprised of an EphA2 targeted monoclonal antibody (1C1) conjugated to a cytotoxin MMAF.

Though MEDI-547 showed promising anti-tumor activity in preclinical models, its toxicology profile included bleeding and coagulation events in non-human species, which were later observed in a Phase I study, resulting in the discontinuation of clinical development. Unlike with MEDI-547, Bicycle did not observe coagulopathy, DIC-like syndrome or changes in closely monitored clotting parameters in preclinical toxicology studies of BT5528. Furthermore, BT5528 and a 1C1-mcMMAF ADC designed to approximate MEDI-547 showed broadly equivalent tumor regression in certain standard tumor models, but BT5528 demonstrated improved efficacy over the ADC in large, poorly vascularized tumor models that are more difficult to treat. These results support the hypothesis that low molecular weight peptide conjugates achieve faster and greater tumor penetration and thus greater efficacy than antibody conjugates.

BT5528 is being evaluated in a Phase I/II multi-center, open-label trial, which is currently enrolling patients with advanced solid tumors in indications associated with EphA2 expression into Phase I dose escalations of BT5528 as a monotherapy and in combination with nivolumab. To date, doses of BT5528 continue to appear well-tolerated with manageable adverse events as the dose escalations approach clinically relevant dose levels.

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 study. 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 statements regarding the clinical development of BT5528 or any of Bicycle's other product candidates or programs; the design of Bicycle's clinical trials; the safety, durability or efficacy of BT5528; and the potential benefits or advantages over other treatments of BT5528 or any of Bicycle's other 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: 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 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; expectations for regulatory approvals to conduct trials or to market product; 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; 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 May 7, 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20200512005437/en/

Investor and Media Contact:
Bicycle Therapeutics
Maren Killackey
maren.killackey@bicycletx.com
+1-617-203-8300

Source: Bicycle Therapeutics plc