Bicycle Therapeutics Announces Pipeline Progress Update

April 7, 2020

- Phase I dose escalation completed for BT1718 —RP2D established and preliminary signs of anti-tumor activity observed, including one partial response

- Dosing complete in second cohort of Phase I dose escalation for BT5528 —all doses administered in Phase I to date appear tolerable

- Significant achievements in multiple partnered programs beyond oncology

- Progress across pipeline continues despite uncertainties associated with coronavirus disease (COVID-19) pandemic —currently, key 2020 events remain on track

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Apr. 7, 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 progress updates across its wholly-owned and partnered programs in oncology and non-oncology indications.

"We and our partners have recently achieved important progress in the advancement of our pipeline that we believe could catalyze the next stage of growth for Bicycle," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "Cancer Research UK has identified a recommended dose, which is within the therapeutic range predicted by preclinical models, for the Phase IIa study of BT1718, which we expect to commence this year. Our next-generation Bicycle Toxin Conjugates (BTCs), BT5528 and BT8009, are quickly progressing through respective stages of development. In addition, we believe our recently announced early discovery collaboration with Genentech will allow us to make considerable investments in expanding our portfolio of immuno-oncology assets, including our wholly-owned programs nearing late preclinical development. Beyond oncology, we continue to make progress on our partnered programs and to execute on our strategy of leveraging our collaborators' expertise in specific therapeutic areas to advance the development of *Bicycle*-based medicines across a broad range of serious diseases."

Dr. Lee continued: "While we expect that the evolving COVID-19 pandemic may impact the pace of clinical development, at this time, we believe the strong progress we've achieved across our pipeline to date will enable us to reach our anticipated 2020 milestones as planned."

BT1718, a potential first-in-class BTC targeting key tumor antigen MT1-MMP

- **Cancer Research UK Completed Phase I Dose Escalation of BT1718 in Patients with Solid Tumors, Established Recommended Phase II Dose (RP2D) at 20 mg/m^2.** The key objectives were met in a Phase I dose escalation sponsored by Cancer Research UK and evaluating safety and tolerability of BT1718 in an unselected group of patients with advanced solid tumors. Based on study results, Cancer Research UK established an RP2D for the expansion cohorts at 20 mg/m^2 administered once weekly. This recommended 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 not a key objective of the Phase I portion of the Phase I/IIa study, preliminary signs of anti-tumor activity were observed during the dose escalation. As reported at the European Society of Medical Oncology (ESMO) 2019 Annual Congress, 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 findings generally remaining consistent as the trial progressed. Today, Bicycle announced that, in addition, one patient with small cell lung cancer experienced a partial response, with a 68% reduction in a target lesion.

  The Company anticipates that Cancer Research UK will initiate the Phase IIa portion of the Phase I/IIa study of BT1718 in 2020, although timing may be dependent on the ongoing COVID-19 pandemic. These expansion cohorts will include patients determined to be MT1-MMP-positive based on a prespecified tumor membrane H-score. Initially, patients will be enrolled into two expansion 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, additional cohorts may be initiated.

BT5528, a BTC targeting EphA2, a potentially high-value target for which antibody-based approaches have been unsuccessful

- **Doses of BT5528 Administered to Date Appear Safe, Well Tolerated in Ongoing Phase I/II Trial.** The second cohort of patients has completed dosing in the Phase I dose escalation portion of a Phase I/II study of BT5528 in patients with advanced solid tumors associated with EphA2 expression. Unlike previous antibody drug conjugate (ADC) programs to target EphA2, BT5528 did not show coagulopathy in preclinical studies. Initial doses of BT5528 administered in the Phase I portion of the study are estimated to deliver six to 12 times the amount of toxin that was delivered by an ADC targeting

EphA2 in an unsuccessful clinical trial and, to date, BT5528 has appeared well tolerated with manageable adverse events.

The Phase I/II multi-center, open-label trial is evaluating BT5528 administered once-weekly as a single agent and in a lagging cohort in combination with nivolumab. The Phase I portion is a dose escalation study primarily designed to assess the safety and tolerability of BT5528 and to determine an RP2D. Bicycle expects the first patient in the combination arm will be dosed in 2020, subject to potential timing and other impacts of the ongoing COVID-19 pandemic.

BT8009, a Nectin-4 targeting BTC with a potentially differentiated profile to marketed ADC

- **Phase I/II Trial of BT8009 Currently On Track to Initiate in 2020.** In preclinical studies, BT8009 demonstrated highly target-dependent and improved anti-tumor activity over comparator Nectin-4-targeting ADCs. Bicycle believes the characteristics of BT8009 may result in a favorable safety profile and could circumvent certain challenges in treating cancers believed to be associated with Nectin-4 expression that are not addressed by current ADC approaches. The Company plans to initiate a Phase I/II study of BT8009 in patients with advanced solid tumors in indications associated with Nectin-4 expression this year, subject to potential timing and other impacts of the ongoing COVID-19 pandemic.

Novel, fully synthetic* Bicycle *systemic immune cell agonists and tumor-targeted immune cell agonists (TICAs™)

- **IND Preparation for BT7480 On Track, Enabling Potential Clinical Start in 2021.** BT7480 is a novel, fully synthetic TICA that contains two *Bicycles,* one targeting Nectin-4 and a second agonizing CD137, that has been shown in preclinical models to rapidly penetrate tumors, effect anti-tumor activity, and facilitate immune memory. IND-enabling activities for BT7480 are ongoing and remain on track to enable the initiation of clinical development in 2021, subject to potential timing and other impacts of the ongoing COVID-19 pandemic.

- **Bicycle Expands IO Pipeline, Selecting BT7455 as New TICA Candidate.** BT7455 is a novel, fully synthetic TICA containing two *Bicycle* arms, one targeting EphA2 and the other agonizing CD137. EphA2 is highly expressed in a number of tumor types of high unmet medical need. In preclinical models, BT7455 exhibits highly potent EphA2-dependent stimulation of CD137 and robust *in vivo* anti-tumor activity against EphA2 expressing tumors.

- **Cancer Research UK Advancing Preclinical Development of BT7401.** BT7401 is a multivalent, systemic immune cell agonist of CD137 built from multiple CD137 monomeric *Bicycles* connected by stable linkers through a central hinge. In 2020, Bicycle announced a second collaboration with Cancer Research UK, in which the organization will fund and sponsor development of BT7401 through a Phase I/IIa clinical study. Preclinical development of BT7401 funded by Cancer Research UK is ongoing.

Partnered programs beyond oncology

- **Oxurion Preparing to Initiate Phase II Trial of Kallikrein Inhibitor Bicycle, THR-149, in Patients with Diabetic Macular Edema (DME).** Positive results from the Phase I clinical trial in patients with DME evaluating the safety and tolerability of THR-149, a novel Bicycle plasma kallikrein (PKal) inhibitor, were announced in 2019. The Phase I data demonstrate that a single intravitreal injection of THR-149 resulted in increasing average improvements in best corrected visual acuity (BCVA) starting at Day 1, which were up to 7.5 letters at Day 14 and maintained through Day 90. No dose-limiting toxicities or drug-related adverse events were reported.

  Oxurion is preparing to initiate a Phase II trial evaluating multiple doses of THR-149 in DME patients who respond sub-optimally to anti-VEGF therapy.

- **Three Target Programs Transitioned to AstraZeneca.** Under the terms of the collaboration, Bicycle is responsible for identifying *Bicycles* for an undisclosed number of respiratory, cardiovascular and metabolic disease targets specified by AstraZeneca. Three target programs have been transitioned to AstraZeneca for subsequent optimization towards potential candidate selection. Pursuant to the collaboration agreement, AstraZeneca is responsible for further development and product commercialization, and Bicycle is eligible for over $1 billion in future R&D funding, development, regulatory and commercialization milestone payments, as well as royalties on sales of products resulting from the partnership.

- **Early Success in Collaboration with Dementia Discovery Fund (DDF).** Bicycle, in collaboration with DDF, is developing *Bicycles* to modulate the activity of proteins implicated in the progression of dementia. The Company has developed *Bicycles* that show successful binding to a target of interest, representing the first part of the first milestone of the collaboration.

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 Bicycle's collaborations with multiple third parties; the discovery, development and potential commercialization of potential product candidates using Bicycle's technology and under collaboration agreements with third-parties; anticipated advancement of preclinical development efforts and initiation and progression of clinical trials; the therapeutic potential for *Bicycles* in various disease applications; the potential impacts of the ongoing COVID-19 pandemic on site initiation, patient enrollment and treatment; and the potential to receive milestone payments and royalties under Bicycle's collaboration agreements. 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; 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; 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; 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-K filed with the Securities and Exchange Commission (SEC) on March 10, 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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