Bicycle Therapeutics Enters Exclusive License and Collaboration Agreement with Ionis to Develop Targeted Oligonucleotide Therapeutics

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- Bicycle to receive a total of $45 million upfront from Ionis and is eligible for development, regulatory and commercial milestone payments and royalties

- The agreement provides Ionis an exclusive license to Bicycles *that bind with high specificity to the transferrin receptor without modifying natural function*

- Bicycle retains rights to use transferrin binding bicycles to deliver all molecular payloads outside of oligonucleotides

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Jul. 13, 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 that Ionis Pharmaceuticals has exercised its option and entered into an exclusive worldwide license and collaboration agreement for tissue-targeted delivery of oligonucleotide therapeutics using *Bicycles* with high affinity to the transferrin receptor (TfR1).

Ionis had an option for an exclusive license under the terms of a December 2020 evaluation and option agreement. The agreement granted Ionis the right to evaluate tissue-targeting TfR1 binding *Bicycles* as vehicles to deliver oligonucleotide therapeutics to specific organ systems and an option to obtain an exclusive license at the end of the evaluation period.

Bicycle receives a total of $45 million upfront, which includes a license fee, an option fee, and an $11 million equity investment. Bicycle is also eligible to receive development, regulatory and commercial milestone payments and royalties for each program developed under the collaboration.

“This agreement stems from a highly successful collaboration with Ionis that began earlier in the year, during which *Bicycles* were shown to selectively deliver oligonucleotide payloads into TfR1-expressing tissue,” said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. “These data build upon our own work, and that of our partners, which have shown *Bicycles* targeted to tumor antigens can rapidly and selectively deliver a variety of payloads into solid tumors. This tissue-targeting payload-delivery capability is facilitated by the unique nature of *Bicycles* that inherently enables the conjugation of a diverse range of molecular cargos without impacting the pharmacology of the target. We believe *Bicycles* have the potential to become the targeting technology of choice for the development of precision medicines.”

Bicycle has identified binders that it believes to be the first small molecules to target TfR1 with high specificity without modifying TfR1’s natural function. These binders present broad conjugation potential across multiple payloads, thereby resulting in the potential to treat diseases in multiple therapeutic areas, including those of the skeletal and cardiac muscles and of the central nervous system. Bicycle is currently also collaborating with the Dementia Discovery Fund (DDF) to advance potential TfR1 *Bicycles* for treating dementia.

Under the terms of the license and collaboration agreement, Ionis and Bicycle will collaborate to develop a pipeline of oligonucleotide therapeutic product candidates delivered using the tissue-targeting TfR1 *Bicycle* technology, while Bicycle retains the rights to use TfR1 *Bicycles* for all non-oligonucleotide therapeutic purposes, including within its existing collaboration with DDF targeting dementia.

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 collaboration with Ionis; the development and potential commercialization of potential product candidates using Bicycle’s technology and under the license and collaboration agreement; the therapeutic potential for *Bicycles* in multiple applications; the potential of Bicycle’s platform to develop potential precision medicines; Bicycle’s continued collaboration with DDF; and the potential to receive milestone payments and royalties under the license and collaboration agreement. 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 Bicycle’s and its collaboration partners’ abilities to meet 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 or its collaboration partners may not realize the intended benefits of Bicycle's 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 studies and trials 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 Bicycle's 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 6, 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 as a result of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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