Bicycle Therapeutics to Present Pharmacokinetic and Safety Evaluation of Lead BTC® Molecules in Phase 1/2 Trials at the 2024 ASCO Annual Meeting

May 23, 2024

Emerging clinical pharmacokinetic and safety profiles of Bicycle Toxin Conjugates® demonstrate differentiation compared to antibody drug conjugates

Trial-in-progress poster outlines registrational Phase 2/3 Duravelo-2 trial of BT8009, a Nectin-4 targeted Bicycle Toxin Conjugate, in patients with locally advanced or metastatic urothelial cancer

Zelenectide pevedotin selected as International Nonproprietary Name for BT8009

FDA Fast Track Designation Granted to BT5528 for the treatment of patients with metastatic urothelial cancer

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--May 23, 2024-- Bicycle Therapeutics plc (NASDAQ: BCYC), a pharmaceutical company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle®) technology, today announced that emerging Phase 1/2 clinical pharmacokinetic (PK) and safety data for Bicycle Toxin Conjugates® (BTC® molecules) BT8009 and BT5528 demonstrating differentiated safety and tolerability profiles will be presented at the 2024 American Society for Clinical Oncology (ASCO) Annual Meeting, taking place May 31-June 4 in Chicago. The company also announced zelenectide pevedotin as the International Nonproprietary Name (INN) for BT8009, and U.S. Food and Drug Administration (FDA) Fast Track Designation granted to BT5528 for the treatment of adult patients with previously treated, locally advanced or metastatic urothelial cancer (mUC).

"As we advance the development of our investigational therapies, we are pleased to see the underlying characteristics of Bicycle® molecules developed using our platform technology — small size for rapid tissue penetration, tunable pharmacokinetics and high target selectivity — are leading to emerging differentiated clinical profiles that we believe have the potential to provide enhanced benefits and quality of life for cancer patients who have advanced disease," said Kevin Lee, Ph.D., CEO of Bicycle Therapeutics. "At ASCO, we look forward to presenting preliminary clinical pharmacokinetic and safety data for our Bicycle Toxin Conjugates zelenectide pevedotin, formerly BT8009, and BT5528 that show substantial differences in their pharmacokinetic profiles compared to antibody drug conjugates. Additionally, we continue to advance enrollment and site activation for our Phase 2/3 Duravelo-2 registrational trial of zelenectide pevedotin in mUC and prepare for multiple clinical and program updates in the second half of 2024. These include updates from the Phase 1/2 clinical trials of zelenectide pevedotin and BT5528, for which the newly awarded FDA Fast Track Designation demonstrates the continued need for targeted therapies for patients living with advanced bladder cancer."

PK and Safety Data from BTC® Molecules
Title: Breaking from the paradigm of antibody-drug conjugates: Evaluation of clinical pharmacokinetics and safety of Bicycle Toxin Conjugates (BTCs)
Poster Session Title: Developmental Therapeutics – Molecularly Targeted Agents and Tumor Biology
Date and Time: Saturday, June 1, at 9 a.m. CT
Abstract Number: 3088
Speaker/Lead Author: Justin Bader, Pharm.D., MBA, Bicycle Therapeutics

Bicycle Therapeutics researchers and collaborators sought to compare PK behavior for BTC molecules to MMAE-containing antibody drug conjugate (ADC) enfortumab vedotin (EV). To do this, the researchers developed PK models and simulated PK exposures over a 28-day cycle for zelenectide pevedotin (5 mg/m^2 once weekly) and BT5528 (5 mg/m^2 once weekly) and compared them to published PK parameters for EV (1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle). Results showed:

- BTC molecule half-life is substantially shorter than that of EV (<1 hour vs 3.6 days), resulting in extensive elimination of the BTC molecule within hours of dose administration rather than weeks. MMAE half-life is also shorter following BTC molecule administration relative to EV (1.9 days vs 2.6 days), potentially due to a slower rate of MMAE release from the ADC.
- Relative to EV, BTC molecules achieved similar unconjugated MMAE PK exposure over a 28-day cycle while maximum serum concentration (Cmax) was elevated for unconjugated MMAE, potentially driving rapid penetration into tumor tissue.
- Relative to EV, conjugated MMAE PK exposure from BTC molecules was substantially lower, potentially limiting toxicities.

Zelenectide pevedotin and BT5528 continued to show promising emerging safety and tolerability profiles, with data to be presented from all patients dosed at Cycle 1 Day 1 with zelenectide pevedotin 5 mg/m^2 once weekly monotherapy (data as of March 22, 2024) and with BT5528 6.5 mg/m^2 every two weeks monotherapy (data as of March 14, 2024). The findings:

- Zelenectide pevedotin-related adverse events (AEs) occurred in 84% of patients, of which 31% were Grade ≥3.
- BT5528-related AEs occurred in 91% of patients, of which 22% were Grade ≥3.
- In contrast to ADCs, treatment-related AEs of interest such as peripheral neuropathy, skin reactions, ocular disorders and hyperglycemia occurred at relatively low frequency and severity with both BTC molecules.

Trial-in-Progress: Registrational Phase 2/3 Duravelo-2 Study

Title: A phase 2/3 study of Bicycle Toxin Conjugate BT8009 targeting Nectin-4 in patients with locally advanced or metastatic urothelial cancer (la/mUC): Duravelo-2
Poster Session Title: Genitourinary Cancer – Kidney and Bladder
Date and Time: Sunday, June 2, at 9 a.m. CT
Abstract Number: TPS4619
Speaker/Lead Author: Yohann Loriot, M.D., Ph.D., Institut de Cancérologie Gustave Roussy, Université Paris-Saclay

The posters will be made available in the Publications section of bicycletherapeutics.com following the presentations.

About Bicycle Therapeutics
Bicycle Therapeutics is a clinical-stage pharmaceutical company developing a novel class of medicines, referred to as Bicycle® molecules, for diseases that are underserved by existing therapeutics. Bicycle molecules 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 Bicycle molecules attractive candidates for drug development. The company is evaluating zelenectide pevedotin, previously BT8009, a Bicycle® Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen; BT5528, a BTC molecule targeting EphA2, a historically undruggable target; and BT7480, a Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®) targeting Nectin-4 and agonizing CD137, in company-sponsored clinical trials. Additionally, the company is developing Bicycle® Radio Conjugates (BRC™) for radiopharmaceutical use and, through various partnerships, is exploring the use of Bicycle® technology to develop therapies for diseases beyond oncology.

Bicycle Therapeutics is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Cambridge, Mass. 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 anticipated progress across its R&D pipeline and the advancement of its product candidates, including zelenectide pevedotin, BT5528 and BT7480; the anticipated progression of Bicycle’s clinical trials and the availability of and timing of announcement of data from clinical trials and program updates for clinical candidates; the development of potential radiopharmaceutical or other product candidates using Bicycle’s technology through various partnerships; the therapeutic potential for Bicycles in oncology and other applications; and Bicycle’s participation in the ASCO annual meeting. 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 research and development and in the initiation, progress and completion of clinical trials and clinical development of Bicycle’s product candidates; the risk that Bicycle may not realize the intended benefits of its technology or partnerships; availability and timing of results from clinical trials; whether the outcomes of preclinical studies will be predictive of clinical trial results; the risk that trials may have unsatisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; 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 2, 2024, 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 because of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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Investors:
Stephanie Yao
SVP, Investor Relations and Corporate Communications
ir@bicycletx.com
857-523-8544

Media:
Deborah Elson
Argot Partners
media@bicycletx.com
212-600-1902

Source: Bicycle Therapeutics plc