Bicycle Therapeutics Reports Recent Business Progress and Third Quarter 2024 Financial Results

October 31, 2024

Presented updated clinical results across oncology pipeline, including a 45% overall response rate (ORR) for zelenectide pevedotin monotherapy and a 45% ORR for BT5528 6.5 mg/m^2 every two weeks monotherapy, both in metastatic urothelial cancer

Progressed radiopharmaceuticals pipeline with first human imaging data validating the potential of MT1-MMP as a novel cancer target and outlined company strategy in this area

Cash and cash equivalents of $890.9 million as of September 30, 2024, excluding $31.7 million UK R&D tax credit received in October 2024; expected financial runway into 2H 2027

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Oct. 31, 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 reported recent business progress and financial results for the third quarter ended September 30, 2024.

“In the third quarter, we continued to make significant advancements across our business and pipeline. At ESMO, we reported updated data for our clinical-stage molecules, further supporting their promising monotherapy response rates and differentiated safety profiles. Additionally, last week we shared exciting first human imaging data for our first radiopharmaceuticals molecule, validating the potential of MT1-MMP as a novel cancer target and providing important information on the ability of our Bicycle molecules to deliver radioisotopes to the tumor,” said Kevin Lee, Ph.D., CEO of Bicycle Therapeutics. “Altogether, we believe these data demonstrate the power and broad capabilities of our Bicycle technology platform, and we look forward to providing additional updates later this year.”

Third Quarter 2024 and Recent Events

- **Announced first human imaging data for a Bicycle Radionuclide Conjugate (BRC®) targeting MT1-MMP and outlined strategy for leadership in next-generation radiopharmaceuticals.**
  - Data presented at the European Association of Nuclear Medicine 2024 Congress validate the potential of MT1-MMP as a novel target in the treatment of cancer, demonstrate the translatability of BRC preclinical data and highlight the potential of Bicycle® molecules for targeted radionuclide therapy.
    - In an oral presentation, the German Cancer Consortium shared results of fluorine-18-labelled FDG-PET/CT imaging and gallium-68-labelled BRC MT1-MMP PET/CT imaging in a 65-year-old male diagnosed with advanced pulmonary adenocarcinoma, the most common type of non-small cell lung cancer, in the lung and lymph nodes confirmed by endobronchial ultrasound biopsy. Both scans revealed multiple lymph node metastases and bone metastases in the sternum. MT1-MMP imaging demonstrated tracer uptake in the primary tumor in the lung and lymph node and bone metastases, consistent with FDG imaging. Additionally, the MT1-MMP BRC tracer showed renal excretion, with all other organs showing only a negligible tracer uptake. Clear imaging contrast was also observed at early time points.
    - In an e-poster presented by Bicycle Therapeutics, preclinical data demonstrate the suitability of Bicycle molecules to deliver indium to tumors *in vivo* due to their favorable properties including specific tumor uptake, rapid tumor penetration and rapid renal elimination. Additionally, imaging showed how the biodistribution profile of BRCs can be optimized to maintain high tumor uptake and retention while significantly reducing kidney levels. These data build on the body of preclinical data that the company has published in this area demonstrating the use of Bicycle molecules to effectively deliver various radioisotopes, such as lutetium and lead, to tumors.
  - Bicycle Therapeutics’ strategy in radiopharmaceuticals focuses on pursuing novel targets with first-in-class potential and selecting the isotope that best aligns with the target biology and indication. In line with this strategy, the company selected EphA2, a novel tumor antigen that is widely expressed in many cancers, as its second BRC target and signed a letter of intent with leading isotope technology company Eckert & Ziegler to put in place an agreement to supply a range of radioisotopes and develop and manufacture BRC molecules.
- **Presented updated clinical results across oncology pipeline at the European Society for Medical Oncology Congress 2024.**

- **Zelenectide pevedotin (formerly BT8009)** is a Bicycle Toxin Conjugate (BTC®) molecule targeting Nectin-4, a well-validated tumor antigen. Updated results from the ongoing Phase 1/2 Duravelo-1 trial evaluating 5 mg/m^2 weekly of zelenectide pevedotin monotherapy in patients with metastatic urothelial cancer (mUC) who had not previously been treated with enfortumab vedotin showed a 45% overall response rate (ORR) in efficacy-evaluable patients (n=38), with a median duration of response of 11.1 months among patients with confirmed responses (n=14). Zelenectide pevedotin continued to demonstrate an emerging differentiated safety profile, particularly around adverse events of interest such as peripheral neuropathy, skin reactions and eye disorders.

  The global Phase 2/3 Duravelo-2 registrational trial of zelenectide pevedotin in patients with mUC is currently enrolling. Additional data updates for zelenectide pevedotin monotherapy in other tumor types and in combination with pembrolizumab in first-line mUC are planned by year end.

- **BT5528** is a BTC molecule targeting tumor antigen EphA2, which has historically been difficult to target using other drug conjugate approaches. Updated results from the ongoing Phase 1/2 trial evaluating 6.5 mg/m^2 every two weeks and 5 mg/m^2 weekly of BT5528 monotherapy in patients with advanced solid tumors showed an emerging differentiated safety profile and antitumor activity, including a 45% ORR in mUC patients enrolled in the dose expansion cohort (n=11) receiving 6.5 mg/m^2 every two weeks.

  Bicycle Therapeutics is currently assessing BT5528 at 6.5 mg/m^2 every two weeks in combination with nivolumab, with results expected in 2025.

- **An analysis of BTC clinical data showed that treatment-related peripheral neuropathy (TRPN) in patients receiving either zelenectide pevedotin or BT5528 occurred at low rates and were primarily low grade.** In 223 patients from ongoing Phase 1/2 studies, TRPN occurred in 28% of zelenectide pevedotin-treated patients and in 19% of BT5528-treated patients, nearly all of which were low grade (Grade 1-2). One Grade 3 event (neuralgia) was reported in a patient treated with zelenectide pevedotin following prior therapy with enfortumab vedotin, while no Grade 3-4 events were observed for BT5528.

  These data showing low rates of TRPN at primarily low severity with BTC molecules support the hypothesis that the antibody-drug construct may be a primary driver of peripheral neuropathy rather than monomethyl auristatin E (MMAE) toxicity as was previously believed.

- **BT7480** is a Nectin-4 targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors. Initial data from the Phase 1/2 dose escalation trial evaluating BT7480 in patients with advanced solid tumors showed an emerging differentiated safety and tolerability profile, with low rates of severe adverse events among 39 patients assigned to receive one of 10 different doses (0.002-3.5 mg/kg weekly). Preliminary biomarker analyses support BT7480 dual targeting of CD137 and Nectin-4 as demonstrated by enhanced immune cell activation, aligned with the proposed mechanism of action of BT7480.

  As the maximum tolerated dose for BT7480 has not yet been reached, Bicycle Therapeutics is continuing dose exploration in combination studies, starting with nivolumab.

- **Promoted Zafar Qadir to Chief Legal Officer and General Counsel.** Since joining Bicycle Therapeutics in April 2020, Mr. Qadir has managed critical responsibilities to support the company's growth by leading the legal, compliance and intellectual property functions. Over the course of his career, Mr. Qadir has more than a decade of corporate, legal, intellectual property, regulatory and compliance experience and has played a pivotal role in Bicycle Therapeutics' key partnerships and transactions.

Third Quarter 2024 Financial Results

- Cash and cash equivalents were $890.9 million as of September 30, 2024, compared to $526.4 million as of December 31, 2023. The increase in cash and cash equivalents is primarily due to net proceeds from our PIPE financing in May 2024 and share option exercises, offset by the repayment of our debt facility with Hercules Capital, Inc. in July 2024 and cash used in operating activities.

- Research and Development (R&D) expenses were $48.3 million for the three months ended September 30, 2024, compared to $39.9 million for the three months ended September 30, 2023. The increase in expense of $8.4 million was primarily due to increased clinical program expenses for zelenectide pevedotin development and increased personnel-related expenses, including incremental share-based compensation of $1.1 million, offset by decreased clinical program

expenses for Bicycle Tumor-Targeted Immune Cell Agonist® molecule development, lower discovery, platform and other expenses, and higher U.K. R&D tax credits period over period.

- General and administrative expenses were $18.3 million for the three months ended September 30, 2024, compared to $16.3 million for the three months ended September 30, 2023. The increase of $2.0 million was primarily due to increased personnel-related expenses, including incremental share-based compensation expense of $0.7 million.

- Net loss was $50.8 million, or $(0.74) basic and diluted net loss per share, for the three months ended September 30, 2024, compared to net loss of $49.9 million, or $(1.26) basic and diluted net loss per share, for three months ended September 30, 2023.

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 (formerly 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 Radionuclide 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 business and its product candidates, including zelenectide pevedotin, BT5528 and BT7480; the anticipated progression of Bicycle’s clinical trials and the timing of announcement of data from clinical trials and program updates for clinical candidates; the development of potential radiopharmaceutical product candidates; the use of Bicycle’s technology through various partnerships to develop potential therapies in diseases beyond oncology; and Bicycle’s expected financial runway. 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; 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; the risk that Bicycle’s projections regarding its expected cash runway are inaccurate or that its conduct of its business requires more cash than anticipated; 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 August 6, 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.

Bicycle Therapeutics plc
Condensed Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share data)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Collaboration revenues	$ 2,676	$ 5,352	$ 31,567	$ 21,645
Operating expenses:				
Research and development	48,265	39,868	123,188	111,799
General and administrative	18,257	16,281	50,588	45,557
Total operating expenses	66,522	56,149	173,776	157,356
Loss from operations	(63,846)	(50,797)	(142,209)	(135,711)
Other income (expense):				
Interest and other income	10,583	3,985	23,981	7,726
Interest expense	(33)	(814)	(1,678)	(2,443)

Loss on extinguishment of debt	(954)	—	(954)	—
Total other income, net	9,596	3,171	21,349	5,283
Net loss before income tax provision	(54,250)	(47,626)	(120,860)	(130,428)
(Benefit from) provision for income taxes	(3,448)	2,272	(3,683)	1,137
Net loss	$ (50,802)	$ (49,898)	$ (117,177)	$ (131,565)
Net loss per share, basic and diluted	$ (0.74)	$ (1.26)	$ (2.15)	$ (3.95)
Weighted average ordinary shares outstanding, basic and diluted	68,988,858	39,576,467	54,566,490	33,291,701

Condensed Consolidated Balance Sheets Data
(In thousands)
(Unaudited)

	September 30, 2024	December 31, 2023
Cash and cash equivalents	$ 890,862	$ 526,423
Working capital	909,789	492,331
Total assets	996,746	595,344
Total shareholders' equity	831,032	370,932

View source version on businesswire.com: https://www.businesswire.com/news/home/20241031404214/en/

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

Matthew DeYoung
Argot Partners
ir@bicycletx.com
212-600-1902

Media:
Jim O'Connell
Weber Shandwick
media@bicycletx.com
312-988-2343

Source: Bicycle Therapeutics plc