Bicycle Therapeutics Reports Recent Business Progress and Fourth Quarter and Full Year 2023 Financial Results

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Catalyst-rich 2024 with multiple clinical data readouts and updates expected for pipeline and discovery programs

Phase 2/3 Duravelo-2 registrational trial for BT8009 in metastatic urothelial cancer now active and recruiting patients

BT8009 initial clinical data showed a promising response and differentiated safety profile

R&D Day outlined near-term strategic priorities and highlighted breadth of Bicycle® platform technology and ability to develop highly differentiated precision therapies for cancer and other diseases

Stephen Sands appointed to Board of Directors

Cash and cash equivalents of $526.4 million as of December 31, 2023, expected to provide financial runway into 2026

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Feb. 20, 2024-- Bicycle Therapeutics plc (NASDAQ: BCYC), a biopharmaceutical company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle®) technology, today reported financial results for the fourth quarter and full year ended December 31, 2023, and provided recent corporate updates.

"2023 was a pivotal year for our company, during which we achieved significant progress across our Nectin-4 and EphA2 clinical oncology portfolios and our discovery pipeline of next-generation Bicycle® molecules, including in radiopharmaceuticals and areas beyond oncology. We continue to demonstrate our ability to develop highly differentiated, precision-guided therapeutics that may offer greater tolerability and lead to enhanced benefit for patients," said Kevin Lee, Ph.D., CEO of Bicycle Therapeutics. "With a catalyst-rich 2024 expected, a strong financial position, validating partnerships and a unique platform technology, we enter this year with significant momentum and focus to advance our mission to help patients not only live longer but also live well."

"I am delighted to welcome Stephen Sands to our Board of Directors," said Pierre Legault, chairman of Bicycle Therapeutics. "He brings a wealth of experience and knowledge that we believe will provide valuable insight and additional depth to our Board as the company enters this new stage of growth and seeks to advance its strategic priorities across multiple key areas."

Corporate Updates and Recent Events

Company Strategy

Outlined strategic priorities at the company's first Research & Development (R&D) Day in December:

- **Execute plan to become a leader in next-generation solid tumor therapeutics and combinations**, which includes:
  - Initiating the Phase 2/3 Duravelo-2 registrational trial for BT8009 in metastatic urothelial cancer (mUC) in 1Q 2024. The trial is now active and recruiting patients.
  - Conducting further clinical studies to assess BT8009, BT7480 and BT5528 in emerging tumors of interest, with data from these studies expected in 2H 2024.

- **Expand opportunities in oncology**, which includes:
  - Advancing the company's next generation of Bicycle Toxin Conjugates ® (BTCs). The company plans to select a BTC® clinical candidate using next-generation technology in 2H 2024.
  - Validating the company's Bicycle ® Radio Conjugates (BRC™) pipeline and partner for success, with updates expected from its wholly owned BRC program by mid-2024.
  - Advancing the company's Bicycle Tumor-Targeted Immune Cell Agonist ® (Bicycle TICA®) immune-oncology pipeline through innovative partnerships.

- **Explore platform potential beyond oncology**, which includes:
  - Continuing the company's strong track record of collaboration.
  - Partnering with leading academic, government and life sciences organizations.

Nectin-4 Portfolio

BT8009 is a BTC® targeting Nectin-4 designed to overcome the significant toxicity associated with other toxin conjugate approaches.

- **Announced Updated BT8009 Clinical Data from the Ongoing Phase 1/2 Duravelo-1 Study Involving Heavily**

Pre-Treated Patients. BT8009 showed: :

- A promising response profile with a 38% objective response rate (ORR) in 26 patients with mUC receiving 5 mg/m^2 weekly and who had not been treated with enfortumab vedotin (EV-naïve), and a median duration of response (mDOR) of 11.1 months in 10 patients with five responders still on therapy.
- Encouraging initial data in other cancers such as ovarian, triple-negative breast (TNBC) and non-small cell lung (NSCLC) that support further expansion beyond mUC.
- An emerging differentiated safety profile seen in 113 patients with various types of cancer receiving 5 mg/m^2 weekly, with treatment-related adverse events being primarily low in frequency and severity.
    - In 34 EV-naïve mUC patients, treatment-related adverse events and adverse events of interest were also low, similar to the 5 mg/m^2 weekly total safety study population. Notably, there were zero cases of severe (≥Grade 3) ocular disorders, peripheral neuropathy or skin reactions that are commonly observed with antibody drug conjugate (ADC) therapies.
    - In seven heavily pre-treated mUC patients receiving BT8009 5 mg/m^2 weekly in combination with pembrolizumab, an acceptable tolerability profile was observed with limited severe treatment-related adverse events, including zero cases of severe (≥Grade 3) ocular disorders, peripheral neuropathy or skin reactions that are commonly observed with ADC therapies.

In 2H 2024, the company plans to complete the Phase 1/2 Duravelo-1 open-label study across multiple cancers and report data from the following cohorts:
° BT8009 5 mg/m^2 weekly in late-line, EV-naive mUCBT8009 5 mg/m^2 weekly in late-line, EV-naive mUC;
° Ovarian, TNBC and NSCLC cancer; and
° BT8009 5 mg/m^2 weekly in combination with pembrolizumab in first-line mUC.

- **BT8009 Selected to Participate in U.S. Food and Drug Administration (FDA) Program to Expedite Commercial Manufacturing Readiness.** In October, Bicycle Therapeutics announced the FDA selected BT8009 to participate in the FDA's new Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) Program, which was created to facilitate CMC development for therapies with expedited clinical development timeframes, based on the anticipated clinical benefits of earlier patient access to the therapy. BT8009 is one of up to nine products selected for the inaugural cohort of the CDRP Program.

BT7480 is a Bicycle TICA® targeting Nectin-4 and agonizing CD137 designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors.

- **Announced Clinical Data from the Phase 1 Clinical Trial.** BT7480 showed:
    - In 33 patients assigned to receive one of nine different doses of BT7480, an emerging differentiated safety and tolerability profile with a low number of severe adverse events. The majority of the patients studied had tumors that expressed Nectin-4 and CD137.
    - Two unconfirmed partial responses in heavily pre-treated patients with cervical cancer.
    - Three prolonged stable disease (≥7 months) in NSCLC and anal cancer.

The company will continue to define the recommended Phase 2 dose (or maximum dose) and dose range for BT7480, with a view to enroll combination cohorts with checkpoint inhibitors in 2024. These data will inform the design of a Phase 2 trial that could support potential accelerated approval of BT7480.

Ephrin-A2 (EphA2) Portfolio

BT5528 is a BTC® targeting EphA2, a historically undruggable target, and is designed to overcome the significant toxicity associated with other toxin conjugate approaches.

- **Announced Clinical Data from Ongoing Phase 1/2 Clinical Trial Enrolling Patients with Various Solid Tumors.** BT5528 showed:
    - In 109 patients, an acceptable emerging tolerability profile with few severe adverse events. Importantly, unlike other EphA2-targeted agents, no bleeding events were observed in patients treated with BT5528 at any dose.
    - Encouraging early activity in mUC with a 39% ORR in 18 patients receiving 6.5 mg/m^2, 8.5 mg/m^2 or 10 mg/m^2 every other week, and an mDOR of four months in seven patients with one responder still on therapy. This includes six partial responses and one unconfirmed response.
    - Encouraging emerging data in other cancers such as ovarian, gastric/upper gastrointestinal and head and neck that are informing the dose optimization strategy and further development.

The company commenced further cohorts in mUC and ovarian cancer to test 5 mg/m^2 weekly, which will inform decisions about dose optimization, potential drug combinations and expansion into other tumor types. Data from these cohorts are expected to be available in the second half of 2024.

Company Updates

Appointed Stephen Sands, Former Chairman of the Global Healthcare Group at Lazard, to the Board of Directors. Mr. Sands has spent more than 35 years at Lazard providing strategic and financial advice to senior executives and boards of directors at leading healthcare and life sciences companies across the globe. Prior to joining Lazard, he was a partner in the healthcare practice of McKinsey & Company. During his career, Mr. Sands has co-founded two life sciences companies: Enzytech (acquired by Alkermes) and Opta Food Ingredients (acquired by Stake Technology and now SunOpta). Mr. Sands has served as director on the boards of several life sciences companies and is currently a director on the board of Cytier Therapeutics (NASDAQ: CYT, Oncology Drugs).

Fourth Quarter and Year End 2023 Financial Results

- Cash and cash equivalents were $526.4 million as of December 31, 2023, compared to $339.2 million as of December 31, 2022. The increase in cash and cash equivalents is primarily due to the receipt of $215.1 million in net proceeds from the underwritten public offering in July 2023, $34.2 million of net proceeds from our ATM offering program and $95.0 million from our collaboration agreements with Novartis and Bayer, offset by cash used in operating activities.

- R&D expenses were $44.7 million for the three months ended December 31, 2023, and $156.5 million for the year ended December 31, 2023, compared to $24.7 million for the three months ended December 31, 2022, and $81.6 million for the year ended December 31, 2022. The increases in expense of $20.0 million and $74.9 million for the three months and year ended December 31, 2023, respectively, were primarily due to increased clinical program expenses for BT8009 development, Bicycle TICA® development and discovery, platform and other expenses, as well as increased personnel-related expenses, including incremental non-cash share-based compensation expense of $0.9 million and $5.2 million for the three months and year ended December 31, 2023, respectively.

- General and administrative expenses were $14.9 million for the three months ended December 31, 2023, and $60.4 million for the year ended December 31, 2023, compared to $10.7 million for the three months ended December 31, 2022, and $49.5 million for the year ended December 31, 2022. The increases of $4.2 million and $10.9 million for the three months and year ended December 31, 2023, respectively, were primarily due to increased personnel-related costs, including incremental non-cash share-based compensation expense of $1.4 million and $0.5 million for the three months and year ended December 31, 2023, respectively, as well as increased professional and consulting fees.

- Net loss was $49.1 million, or $(1.16) basic and diluted net loss per share, for the three months ended December 31, 2023, and net loss was $180.7 million, or $(5.08) basic and diluted net loss per share, for the year ended December 31, 2023, compared to net loss of $30.0 million or $(1.01) basic and diluted net loss per share, for three months ended December 31, 2022, and net loss of $112.7 million or $(3.80) basic and diluted net loss per share, for the year ended December 31, 2022..

About Bicycle Therapeutics

Bicycle Therapeutics is a clinical-stage biopharmaceutical 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 BT8009, a Bicycle® Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen; BT5528, a BTC 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 advancement of its product candidates, including BT8009, BT5528 and BT7480; the anticipated progression of Bicycle’s clinical trials, including the timing of patient dosing in the Duravelo-2 Phase 2/3 clinical trial; anticipated clinical and other benefits of Bicycle Therapeutics’ participation in the CDRP Program; the availability of and timing of announcement of data from clinical trials and regulatory updates for clinical candidates the discovery, development and potential commercialization of potential radiopharmaceutical or other product candidates using Bicycle’s technology under the strategic collaboration agreements; BT8009’s potential to be a transformative therapy for patients with metastatic bladder cancer; the therapeutic potential for Bicycles in oncology and other applications; Bicycle’s goal to become a leader in next-generation solid tumor therapeutics and combinations; Bicycle’s expected financial runway; and the potential benefits of appointing Stephen Sands to Bicycle’s Board of Directors. 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, 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 strategic collaborations; availability and timing of results from 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 trials may have unsatisfactory outcomes; challenges or delays in the development and preparation of the commercial manufacturing readiness of BT8009; 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; the risk that the intended benefits from the appointment of Stephen Sands to Bicycle's Board of Directors may not be realized; 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 November 2, 2023, 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 December 31,		Year Ended December 31,	
	2023	2022	2023	2022
Collaboration revenues	$ 5,331	$ 3,185	$ 26,976	$ 14,463
Operating expenses:				
Research and development	44,697	24,719	156,496	81,609
General and administrative	14,869	10,677	60,426	49,507
Total operating expenses	59,566	35,396	216,922	131,116
Loss from operations	(54,235)	(32,211)	(189,946)	(116,653)
Other income (expense):				
Interest income	6,276	2,639	14,002	5,756
Interest expense	(820)	(826)	(3,263)	(3,344)
Total other income (expense), net	5,456	1,813	10,739	2,412
Net loss before income tax provision	(48,779)	(30,398)	(179,207)	(114,241)
Provision for (benefit from) income taxes	320	(420)	1,457	(1,524)
Net loss	$ (49,099)	$ (29,978)	$ (180,664)	$ (112,717)
Net loss per share, basic and diluted	$ (1.16)	$ (1.01)	$ (5.08)	$ (3.80)
Weighted average ordinary shares outstanding, basic and diluted	42,419,326	29,711,570	35,592,362	29,660,659

Balance Sheets Data
(In thousands)
(Unaudited)

	December 31, 2023	December 31, 2022
Cash and cash equivalents	$ 526,423	$ 339,154
Working capital	492,331	316,041
Total assets	595,344	410,609
Total shareholders' equity	370,932	270,783

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