Bicycle Therapeutics Reports Recent Business Progress and Fourth Quarter and Full Year 2024 Financial Results

February 25, 2025

Updated topline Phase 1 combination data for zelenectide pevedotin plus pembrolizumab continue to show promising anti-tumor activity and a differentiated safety profile in first-line metastatic urothelial cancer; Duravelo-2 dose selection data expected in 2H 2025

Enhanced response to zelenectide pevedotin seen in NECTIN4 gene-amplified late-line breast cancer and non-small cell lung cancer (NSCLC), resulting in U.S. FDA Fast Track designations for triple-negative breast cancer and NSCLC; several Phase 1/2 trials expected to start in 2025

Advancing radiopharmaceuticals pipeline, with additional MT1-MMP human imaging data expected in mid-2025 and first EphA2 human imaging data planned for 2H 2025

Cash and cash equivalents of $879.5 million as of December 31, 2024, expected to provide financial runway into 2H 2027

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Feb. 25, 2025-- 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 financial results for the fourth quarter and full year ended December 31, 2024, and provided recent corporate updates.

“In 2024, the significant progress across our pipeline and business continued to validate our approach to developing next-generation precision-guided therapeutics. We believe that zelenectide pevedotin’s promising anti-tumor activity and differentiated safety profile could transform the treatment landscape not only for patients with metastatic urothelial cancer but also NECTIN4 gene-amplified solid tumors. Additionally, our encouraging first human imaging data for MT1-MMP demonstrates the potential of our technology platform to produce radiopharmaceutical medicines to novel targets,” said Bicycle Therapeutics CEO Kevin Lee, Ph.D. “With a clear strategy to build on this foundation and financial runway into the second half of 2027, we are strongly positioned for another year of execution across our research and development pipeline of oncology, radiopharmaceuticals and partnered programs as we work to bring innovative therapies to cancer patients.”

Fourth Quarter 2024 and Recent Events

- **Announced updated topline combination data for zelenectide pevedotin plus pembrolizumab in first-line metastatic urothelial cancer (mUC).** As of Jan. 3, 2025, updated topline results from the ongoing Phase 1 Duravelo-1 trial evaluating zelenectide pevedotin 5 mg/m^2 weekly plus pembrolizumab 200 mg once every 3 weeks in 22 first-line cisplatin-ineligible patients with mUC continued to show promising anti-tumor activity and a differentiated safety profile.
  - Among 20 efficacy evaluable patients, a 65% overall response rate (ORR) (13/20) was achieved, and a 50% ORR (10/20) was reached among patients with confirmed responses. Of the 3 unconfirmed responses, 1 patient remained on treatment at the time of the reported clinical results.
  - Median duration of response (mDOR) is not yet mature, with 12 patients still on treatment at the time of the reported clinical results.
  - The safety and tolerability profile continues to be broadly consistent with other Phase 1 zelenectide pevedotin monotherapy and combination cohorts. Adverse events of clinical interest such as peripheral neuropathy, skin reactions and eye disorders were primarily low grade. All cases of Grade 3 treatment-related adverse events (TRAEs) of clinical interest were reversible, and there were no Grade 4 or Grade 5 TRAEs of clinical interest.

  Bicycle Therapeutics is currently conducting the Phase 2/3 Duravelo-2 registrational trial evaluating zelenectide pevedotin plus pembrolizumab versus chemotherapy in first-line mUC (Cohort 1), and zelenectide pevedotin monotherapy and in combination with pembrolizumab in late-line mUC (Cohort 2). In each cohort, two doses of zelenectide pevedotin – 5 mg/m^2 weekly and 6 mg/m^2 two weeks on, one week off – are being assessed before a planned final dose selection in 2H 2025.

- **Announced development strategy leveraging NECTIN4 gene amplification for zelenectide pevedotin in breast cancer, lung cancer and multiple tumor types.** During the 2024 San Antonio Breast Conference Symposium, Bicycle Therapeutics presented data from post-hoc analyses of late-line breast cancer and lung cancer patients enrolled in the Phase 1/2 Duravelo-1 trial evaluating zelenectide pevedotin 5 mg/m^2 weekly. Results showed enhanced anti-tumor activity of zelenectide pevedotin monotherapy in patients with NECTIN4 gene amplification and/or polysomy.
  - Among 38 breast cancer patients enrolled, 35 patients were efficacy evaluable. Additionally, 23 breast cancer patient samples were available for NECTIN4 testing, of which 8 demonstrated NECTIN4 gene amplification or harbored NECTIN4 polysomy. Results showed a 62.5% ORR (5/8) in patients with NECTIN4 gene amplification and/or polysomy versus 14.3% ORR (5/35) in efficacy-evaluable patients. All responses were seen in patients with NECTIN4 gene amplification and/or polysomy.
  - Among 32 triple-negative breast cancer (TNBC) patients enrolled, 30 patients were efficacy evaluable. Additionally,

19 TNBC patient samples were available for NECTIN4 testing, of which 7 demonstrated NECTIN4 gene amplification or harbored a NECTIN4 polysomy. Results showed a 57.1% ORR (4/7) in patients with NECTIN4 gene amplification and/or polysomy versus 13.3% ORR (4/30) in efficacy-evaluable patients. All responses were seen in patients with NECTIN4 gene amplification and/or polysomy. Notably, all 3 patients with NECTIN4 gene amplification who responded to zelenectide pevedotin had prior treatment with sacituzumab govitecan.

- Among 40 non-small cell lung cancer (NSCLC) patients enrolled, 34 patients were efficacy evaluable. Additionally, 19 NSCLC patient samples were available for NECTIN4 testing, of which 6 demonstrated NECTIN4 gene amplification. Five out of 6 patients with NECTIN4 gene amplification were efficacy evaluable. Results showed a 40.0% ORR (2/5) in patients with NECTIN4 gene amplification versus 8.8% ORR (3/34) among efficacy-evaluable patients. Of the 3 partial responses, 2 were confirmed and 1 was unconfirmed. Two out of 3 responses were seen in patients with NECTIN4 gene amplification.

Zelenectide pevedotin was generally well tolerated, demonstrating a safety and tolerability profile consistent with data from other Duravelo-1 cohorts, and TRAEs were primarily low grade, further supporting the potential for NECTIN4 gene amplification to serve as a biomarker for therapy stratification. Based on these data, the U.S. Food and Drug Administration (FDA) granted Fast Track designation to zelenectide pevedotin for the treatment of adult patients with previously treated, NECTIN4 gene-amplified, advanced or metastatic TNBC and NSCLC.

Bicycle Therapeutics has continued to build a robust patent estate related to the use of NECTIN4 gene amplification as a biomarker for patient selection. The company plans to initiate several additional Phase 1/2 trials evaluating zelenectide pevedotin in NECTIN4 gene-amplified cancer, including breast cancer (Duravelo-3) in 1H 2025 and lung cancer (Duravelo-4) and multi-tumor (Duravelo-5) in 2H 2025.

- **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 (DKTK) 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 NSCLC, in the lung and lymph nodes. 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.
  - Preclinical data presented by Bicycle Therapeutics demonstrated 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.

Bicycle Therapeutics continues to advance its emerging BRC pipeline, with additional MT1-MMP human imaging data anticipated in mid-2025 and initial EphA2 human imaging data expected in 2H 2025. The company is targeting clinical trials for its first radiotherapeutic program to begin in 2026.

- **Expanded Clinical Advisory Board with the appointment of three distinguished oncology experts to further support the advancement of the company's clinical programs.** Bicycle Therapeutics welcomed Howard A. "Skip" Burris, III, M.D., president and chief medical officer of Sarah Cannon Research Institute; Markus Eckstein, M.D., a board-certified senior consultant pathologist at the University Hospital Erlangen (FAU Erlangen-Nürnberg); and Niklas Klümper, M.D., senior consultant for Urology & Genitourinary Oncology at the University Hospital Bonn.

Participation in Upcoming Investor Conferences

Bicycle Therapeutics management will participate in a fireside chat at the TD Cowen 45th Annual Health Care Conference on Tuesday, March 4, at 9:50 a.m. ET. A live webcast of the fireside chat will be accessible from the Investor section of the company's website at www.bicycletherapeutics.com. A replay of the webcast will be archived and available following the event.

Fourth Quarter and Year End 2024 Financial Results

- Cash and cash equivalents were $879.5 million as of December 31, 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 the company's private investment in public equity (PIPE) financing in May 2024 and share option exercises, offset by the repayment of the company's debt facility with Hercules Capital, Inc. in July 2024 and cash used in operating activities.
- Research and development (R&D) expenses were $49.8 million for the three months ended December 31, 2024, and $173.0 million for the year ended December 31, 2024, compared to $44.7 million for the three months ended December 31, 2023, and $156.5 million for the year ended December 31, 2023. The increases in expense of $5.1 million and $16.5 million for the three months and year ended December 31, 2024, respectively, were primarily due to increased clinical program expenses for zelenectide pevedotin development and increased personnel-related expenses, including

incremental share-based compensation expense of $2.2 million and $3.8 million for the three months and year ended December 31, 2024, respectively, 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 $21.6 million for the three months ended December 31, 2024, and $72.2 million for the year ended December 31, 2024, compared to $14.9 million for the three months ended December 31, 2023, and $60.4 million for the year ended December 31, 2023. The increases of $6.7 million and $11.8 million for the three months and year ended December 31, 2024, respectively, were primarily due to increased personnel-related expenses, including incremental share-based compensation expense $0.3 million and $1.8 million for the three months and year ended December 31, 2024, respectively, as well as increased professional and consulting fees.
- Net loss was $51.9 million, or $(0.75) basic and diluted net loss per share, for the three months ended December 31, 2024, and net loss was $169.0 million, or $(2.90) basic and diluted net loss per share, for the year ended December 31, 2024, compared to net loss of $49.1 million or $(1.16) basic and diluted net loss per share, for three months ended December 31, 2023, and net loss of $180.7 million or $(5.08) basic and diluted net loss per share, for the year ended December 31, 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 www.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 the potential for zelenectide pevedotin to transform the treatment landscape for patients with mUC and NECTIN4 gene-amplified solid tumors; the potential for Bicycle Therapeutics’ technology to produce radiopharmaceutical medicines; the company’s ability to build on its foundation, including with respect to execution across its pipeline; the planned dose selection for Duravelo-2; the anticipated initiation of clinical trials of zelenectide pevedotin in breast cancer, lung cancer and multi-tumor types and of the company’s first radiotherapeutic program; the timing of announcement of human imaging data for MT1-MMP and EphA2 targeting BRCs; expectations with respect to Bicycle Therapeutics’ financial runway; and the use of Bicycle Therapeutics’ technology through various partnerships to develop potential therapies in diseases beyond oncology. Bicycle Therapeutics 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 Therapeutics’ product candidates; the risk that Bicycle Therapeutics may not realize the intended benefits of its technology, partnerships or NECTIN4 gene-amplification strategy; the risk that Bicycle Therapeutics may not achieve any of its clinical development strategies; timing of results from clinical trials; whether the outcomes of preclinical studies and prior clinical trials will be predictive of future clinical trial results; the risk that trials may have unsatisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle Therapeutics’ product candidates; the risk that Bicycle Therapeutics’ 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 Therapeutics’ 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 Therapeutics’ Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on October 31, 2024, as well as in other filings Bicycle Therapeutics 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 Therapeutics 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,	
	2024	2023	2024	2023
Collaboration revenue	$ 3,708	$ 5,331	$ 35,275	$ 26,976
Operating expenses:				

Research and development	49,778	44,697	172,966	156,496
General and administrative	21,593	14,869	72,181	60,426
Total operating expenses	71,371	59,566	245,147	216,922
Loss from operations	(67,663)	(54,235)	(209,872)	(189,946)
Other income (expense):				
Interest and other income	10,303	6,276	34,284	14,002
Interest expense	(52)	(820)	(1,730)	(3,263)
Loss on extinguishment of debt	—	—	(954)	—
Gain on extinguishment of research and development funding liability	4,476	—	4,476	—
Total other income, net	14,727	5,456	36,076	10,739
Net loss before income tax provision	(52,936)	(48,779)	(173,796)	(179,207)
(Benefit from) provision for income taxes	(1,082)	320	(4,765)	1,457
Net loss	$ (51,854)	$ (49,099)	$ (169,031)	$ (180,664)
Net loss per share, basic and diluted	$ (0.75)	$ (1.16)	$ (2.90)	$ (5.08)
Weighted average ordinary shares outstanding, basic and diluted	69,051,745	42,419,326	58,207,593	35,592,362

Balance Sheets Data
(In thousands)
(Unaudited)

	December 31, 2024	December 31, 2023
Cash and cash equivalents	$ 879,520	$ 526,423
Working capital	861,375	492,331
Total assets	956,868	595,344
Total shareholders' equity	793,060	370,932

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Source: Bicycle Therapeutics plc