Bicycle Therapeutics Provides Update on Nuzefatide Pevedotin and EphA2 Pipeline at the AACR Annual Meeting 2026

April 20, 2026

Phase 1 combination data of 6.5mg/m^2 Q2W nuzefatide pevedotin plus nivolumab demonstrate an encouraging preliminary efficacy profile with a differentiated tolerability profile in previously treated metastatic urothelial cancer

Nuzefatide pevedotin demonstrates potent preclinical anti-tumor activity across a broad range of pancreatic ductal adenocarcinoma (PDAC) and head and neck squamous cell carcinoma xenograft models

Dose range finding studies identify 8mg/m^2 Q2W as the preferred dose for monotherapy and first patient dosed in 2L+ PDAC Phase 2 trial

Human imaging data provides further evidence of the potential of EphA2 as a novel cancer target and the positive properties of Bicycle® radioligand molecules for radiopharmaceutical use

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Apr. 20, 2026-- 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 updates from its EphA2 pipeline at the American Association for Cancer Research (AACR) Annual Meeting 2026.

“EphA2 is a potentially high value target that is widely expressed in cancer and has been considered undruggable following the failure of multiple antibody-based approaches due to toxicity or insufficient efficacy. Encouraging results presented at AACR demonstrate the potential of our Bicycle platform to drug this target with a generally well tolerated and differentiated safety profile and enhances our understanding of how best to deploy EphA2-targeted therapeutics,” said Bicycle Therapeutics CEO Kevin Lee, Ph.D. “Nuzefatide pevedotin has demonstrated an emerging differentiated safety profile as a monotherapy and in combination with a checkpoint inhibitor, in over 150 patients to date. Consequently, using a combination of expression analysis, preclinical patient-derived xenograft efficacy studies, and human patient imaging, we have identified significant opportunities for this molecule in a number of cancers, including pancreatic cancer.”

Dr. Lee added: “We have now identified 8mg/m^2 Q2W as the preferred dose for monotherapy. Our strategy is to initially develop nuzefatide in pancreatic cancer where patients have limited available treatment options, and in parallel, to bring forward the next generation of EphA2-targeted radiotherapeutics to build on our foundational work in bladder and other EphA2-expressing tumors. Following this strategy, I am very pleased to announce that the first patient in our 2L+ pancreatic ductal adenocarcinoma Phase 2 study has been successfully dosed.”

AACR Annual Meeting 2026 Data Highlights

- **Nuzefatide pevedotin (nuzefatide), formerly BT5528, a potentially first-in-class EphA2 targeting Bicycle® Drug Conjugate (BDC®), Phase 1/2 data in combination with nivolumab in metastatic urothelial cancer (mUC) patients.** As of the February 9, 2026 data cutoff, results from the Phase 1/2 trial evaluating nuzefatide 6.5mg/m^2 once every two weeks (Q2W) plus nivolumab 480mg once every four weeks (Q4W) in 14 patients with mUC who had previously progressed on a checkpoint inhibitor (10 while on enfortumab vedotin) showed:
  - 40% confirmed overall response rate (ORR) (4/10) among patients with EphA2+ tumors and 100% confirmed ORR (3/3) among patients with EphA2+ tumors that were monomethyl auristatin E (MMAE)-naïve.
  - Patients who achieved a partial response (PR) or at least 16 weeks of stable disease (SD) were on treatment for a minimum of 56 weeks and most continued on treatment at the time of the data cut-off.
  - Nuzefatide in combination with nivolumab was generally well tolerated with no Grade ≥3 treatment-related adverse events (TRAEs) of clinical interest and no TRAEs of haemorrhage observed. Only one dose-limiting toxicity of Grade 3 fatigue that lasted for five days was reported and improved to Grade 1 without dose reduction.

  In contrast to other EphA2-targeted agents, nuzefatide has demonstrated a positive emerging efficacy and safety profile in over 150 patients with hard-to-treat tumors to date. Further work has led Bicycle Therapeutics to determine 8mg/m^2 Q2W as the preferred dose for the Phase 2 trial in patients with recurrent pancreatic ductal adenocarcinoma (PDAC).

- **Additional human imaging data of a Bicycle® Imaging Agent (BIA) targeting EphA2 in patients with PDAC.** The German Cancer Consortium (DKTK), part of a cooperative network with the German Cancer Research Center (DKFZ), presented human imaging data conducted with a Bicycle molecule targeting EphA2 labelled with gallium-68 (EphA2 BIA). Seven patients with histologically confirmed PDAC underwent PET/CT imaging up to three hours post injection of the EphA2 BIA. Data demonstrated rapid tumor uptake and excretion primarily via the kidneys in six out of seven patients. EphA2 BIA PET imaging successfully detected multiple liver, bone, lymph node, and peritoneal metastases.

  These data are representative of the results seen in 15 out of 18 patients with PDAC who have undergone EphA2 BIA

imaging to date. Bicycle Therapeutics believes these data validate the potential of EphA2 as a novel target in the treatment of cancer, demonstrate the translatability of preclinical data and highlight the potential of Bicycle® molecules for targeted radioligand therapies and radiopharmaceutical imaging.

- **Preclinical assessment of nuzefatide anti-tumor activity in patient-derived xenograft (PDX) models of PDAC.** Expression of EphA2 was found in all 16 PDAC PDX models. Of the 14 PDAC PDX models assessed for anti-tumor activity, 10 models were sensitive to nuzefatide, six of which showed high sensitivity. These data support the potential for nuzefatide to offer a novel option for the treatment of patients with PDAC.

  In March 2026, Bicycle Therapeutics began enrolling patients in a Phase 2 clinical trial to evaluate efficacy, safety, and pharmacokinetics of nuzefatide in adult patients with recurrent PDAC, and the first patient was successfully dosed in April 2026.

- **Preclinical assessment of nuzefatide anti-tumor activity in cell-line-derived xenograft (CDX) models of head and neck squamous cell carcinoma (HNSCC).** Nuzefatide demonstrated potent preclinical anti-tumor activity in EphA2-expressing CDX models of HNSCC.

The presentations are available in the Publications section of the Bicycle Therapeutics website.

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 nuzefatide pevedotin, formerly BT5528, a Bicycle® Drug Conjugate (BDC®) targeting EphA2, a historically undruggable target; a pipeline of other bicycle-based conjugate molecules, including Bicycle® Radioconjugates (BRC®) for radiopharmaceutical use; zelenectide pevedotin (formerly BT8009), a BDC® targeting Nectin-4, a well-validated tumor antigen; BT7480, a Bicycle Tumor-Targeted Immune Cell Agonist® (Bicycle TICA®) targeting Nectin-4 and agonizing CD137; and, through various partnerships, is exploring the use of Bicycle® technology to develop therapies for diseases in additional therapeutic areas.

Bicycle Therapeutics is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Lexington, 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: the potential therapeutic benefit of nuzefatide pevedotin, including the reproducibility and durability of any favorable results initially seen in patients dosed to date in clinical trials, and the potential development of nuzefatide pevedotin in a number of cancers, including pancreatic cancer; the progress of Bicycle Therapeutics’ clinical trials, reporting data from Bicycle Therapeutics’ clinical trials, including for nuzefatide pevedotin, the timing of EphA2 human imaging data and updates on future clinical development plans for nuzefatide pevedotin; the potential of EphA2 as a novel cancer target and the positive properties of Bicycle® radioligand molecules for radiopharmaceutical use; the potential of the Bicycle platform to drug EphA2 and to enhance understanding of how best to deploy EphA2 targeted therapeutics; and the development of the Bicycle® radioligands pipeline, including BRCs and BIAs. 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: the recently announced workforce reduction may take longer or result in more significant charges or cash expenditures than anticipated or otherwise negatively impact Bicycle Therapeutics’ and its business plans during and after the period during which the proposed workforce reduction is being executed; uncertainties related to the benefits of the recently announced strategic reprioritization; 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 or partnerships; 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’ Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 17, 2026, 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.

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