A Phase 2 study of zelenectide pevedotin, a Bicycle® Drug Conjugate (BDC®), in patients with *NECTIN4* amplified advanced breast cancer (Duravelo-3)

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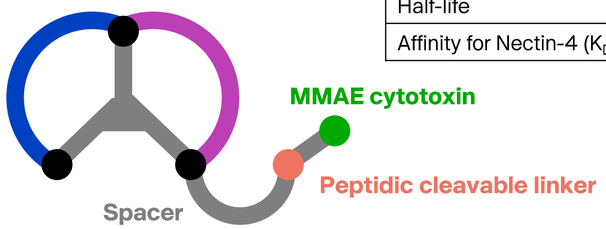
BACKGROUND

- Bicycle® molecules are an innovative therapeutic class under clinical evaluation that offers the manufacturing and pharmacokinetic properties of a small molecule with the high binding specificity of a biologic,[1–3] making them ideally suited for the targeted delivery of a range of payloads, such as cytotoxins, to solid tumours
- Zelenectide pevedotin (formerly BT8009), is a first-in-class Bicycle® Drug Conjugate (BDC®), comprised of a highly selective bicyclic peptide targeting Nectin-4 conjugated to monomethyl auristatin E (MMAE) via a cleavable linker (**Figure 1**)[4]
- Bicycle® molecules have lower molecular weight and shorter plasma half-life than antibody-drug conjugates, with distinct pharmacokinetics/dynamics, i.e., potential for rapid tumour penetration and minimal healthy tissue exposure[4–7]

Figure 1: SCHEMATIC AND CHARACTERISTICS OF ZELENECTIDE PEVEDOTIN[4,6,7]



Molecular weight	4.2 kDa
Half-life	<1 hr
Affinity for Nectin-4 (K_D)	2.5 nM

- *NECTIN4* amplification has been proposed as a predictive biomarker of response to Nectin-4 targeted therapy in mUC[8]
- An analysis of *NECTIN4* amplification in a large, independent cohort of 245 patients with BC revealed that *NECTIN4* amplification is common: 19% (30/161), 14% (5/36), and 23% (11/48) of patients with HR+/HER2-, HER2+, and TNBC, respectively[9]
- In the Duravelo-1 study, *NECTIN4* amplification appeared to show predictive clinical utility in identifying patients with metastatic BC who had an enhanced response to zelenectide pevedotin with an ORR of 62.5% (5/7) in *NECTIN4* amplified patients including polysomy versus an ORR of 14.3% (5/38) in biomarker unselected patients with metastatic BC[10]
  - *NECTIN4* amplification, determined by FISH testing, was performed on archival tissue from patients with BC who had available tumour tissue and who had consented to optional future research
  - *NECTIN4* amplification was defined as a ratio of *NECTIN4:CEN1* of ≥2; testing was performed at a laboratory accredited under DIN EN ISO/IEC 17020, using a standard protocol, as previously described[8]

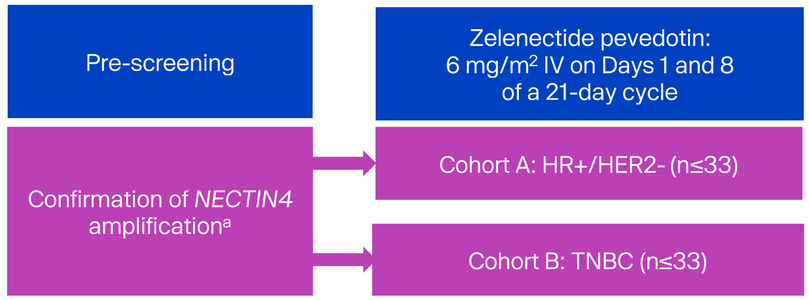
OBJECTIVES

- Duravelo-3 (NCT06840483; BT8009-201) aims to evaluate the efficacy and safety of zelenectide pevedotin monotherapy in patients with recurrent unresectable or metastatic *NECTIN4* amplified BC

Open label · **Phase 2** · **Global** · **Multicentre**

TRIAL DESIGN

Figure 2: DURAVELO-3 (BT8009-201) STUDY DESIGN



[a]Assessed centrally from archival or fresh tumour tissue.

CURRENT STATUS

Opened to enrolment Q1 of 2025 and is actively recruiting.

For additional information on the study, please contact **clinicalstudies@bicycletx.com**

STUDY ENDPOINTS

Primary:

- Objective response rate (Investigator assessed per RECIST v1.1)

Secondary:

- Safety and tolerability (incidence of TEAE per NCI CTCAE v5.0)
- Duration of response, disease control rate, clinical benefit rate, progression-free survival, and time to progression (Investigator assessed per RECIST v1.1)
- Overall survival

Exploratory:

- Tumour and peripheral biomarkers
  - Nectin-4 expression
  - Surrogates of *NECTIN4* amplification (e.g. *SDHC*)
  - Markers of resistance
  - Pharmacogenomics
  - Circulating Nectin-4 protein and ctDNA
- Objective response rate, duration of response, and TEAEs by *NECTIN4* amplification status
- Pharmacokinetics of zelenectide pevedotin and MMAE
- Incidence of anti-drug antibody

KEY ELIGIBILITY CRITERIA

Inclusion

- Aged ≥18 years
- ECOG performance status 0–1
- Adequate organ and haematological function, including eGFR ≥30 mL/min
- Archival or fresh tumour tissue available for biomarker testing
- Confirmed *NECTIN4* amplification

Cohort A only:

- Histologically or cytologically confirmed HR+/HER2- BC
- Received 1–3 prior lines of non-endocrine therapy for unresectable or metastatic BC[a]

Cohort B only:

- Histologically or cytologically confirmed TNBC
- Received 1–3 prior lines of systemic therapy for unresectable or metastatic BC[a]

[a]May include a topoisomerase inhibitor, unless contraindicated.

Exclusion

- Prior treatment with MMAE-based therapy
- Previously tested HER2+ (IHC 3+ or ISH+)
- Prior systemic anti-cancer therapy or investigational agent within 28 days or 5 half-lives
- Uncontrolled diabetes (HbA1c ≥8%), hypertension, pleural or pericardial effusion, or ascites
- Active infection, interstitial lung disease, or pneumonitis
- Active keratitis/corneal ulcerations; or active/untreated CNS metastases
  - Patients with treated brain metastases may participate if stable for at least 4 weeks prior to the first dose, and are without any symptoms that would confound the evaluation of neurologic or other AEs
- Ongoing Grade ≥2 toxicity associated with prior treatment for BC, especially peripheral neuropathy

ABBREVIATIONS

AEs, adverse events; BC, breast cancer; BDC®, Bicycle® Drug Conjugate; CNS, central nervous system; ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; FISH, fluorescence in situ hybridisation; HbA1c, haemoglobin A1c; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridisation; IV, intravenous; MMAE, monomethyl auristatin E; mUC, metastatic urothelial carcinoma; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Q1, quarter one; RECIST, Response Evaluation Criteria in Solid Tumours; *SDHC*, succinate dehydrogenase subunit C; TEAE, treatment-emergent adverse events; TNBC, triple negative breast cancer.

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