Breaking from the paradigm of antibody-drug conjugates: Evaluation of clinical pharmacokinetics and safety of Bicycle Toxin Conjugates® (BTCs)

Abstract ▶ 3088

Justin Bader, PharmD, MBA[1], Meredith McKean, MD, MPH[2], Leslie R. DeMars, MD[1], Yasong Lu, PhD[1], Mengyao Li, PhD[1], Amy Dickson, MS[1], Gavin Bennett, PhD[3], Santiago Arroyo, MD, PhD[1], Elisa Fontana, MD, PhD[4], Louise Carter, MBBS, PhD[5], Jordi Rodón, MD, PhD[6], Gerald S. Falchook, MD[7], Hongmei Xu, PhD[1]

[1]Bicycle Therapeutics, Inc., Cambridge, MA, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]BicycleTx Ltd, Cambridge, UK; [4]Sarah Cannon Research Institute UK, London, UK; [5]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA.

BACKGROUND

- Bicycle Toxin Conjugates® (BTCs) are chemically synthesized molecules comprising a small bicyclic peptide linked to a cytotoxin[1,2]
- Zelenectide pevedotin (zel [BT8009]) and BT5528 are BTCs linked to monomethyl auristatin E (MMAE) that target Nectin-4 and EphA2, respectively, and have shown preliminary antitumor activity[1,3,4]
- BTCs are a unique therapeutic class of small size (~4.0–4.5 kDa)[1,2,4], with pharmacokinetic (PK) properties distinct from antibody-drug conjugates (ADCs)[2]
- ADCs containing MMAE demonstrate antitumor efficacy but have notable safety issues (e.g., skin rash, neuropathy, and hyperglycemia), which have been attributed to their slow clearance, leading to increased uptake into off-target tissues and increased exposure to plasma proteases, which cause off-target payload release[2,5,6]
- To evaluate BTC® PK and safety, we present results of the ongoing phase 1/2 trials for zel (BT8009) (NCT04561362) and BT5528 (NCT04180371)

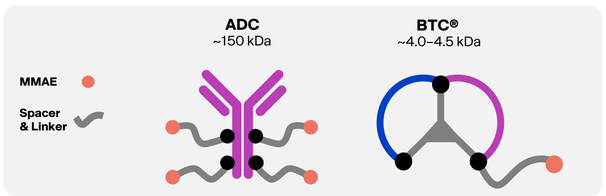
METHODS

- Across trials, patients with advanced solid tumors receiving intravenous zel (BT8009) (n=183) monotherapy or BT5528 (n=128) monotherapy were evaluated
- Dose and schedule of drug in these studies:
  - 2.5, 5.0, or 7.5 mg/m^2 weekly (QW), 7.5 or 10.0 mg/m^2 every 2 weeks (Q2W), or 7.5 mg/m^2 2 weeks on/1 week off for zel (BT8009)
  - 2.2, 4.4, 5.0, 6.5, or 8.5 mg/m^2 QW, or 6.5, 8.5 or 10.0 mg/m^2 Q2W for BT5528
- Of the total patient population, 149 patients were treated with the recommended phase 2 dose (RP2D) of zel (BT8009) at 5 mg/m^2 QW and 74 with the RP2D of BT5528 at 6.5 mg/m^2 Q2W (safety analysis population)

Pharmacokinetics

- Population PK models for zel (BT8009) and BT5528 were developed, and PK exposures (Cycle 1 area under the concentration curve [AUC]) were simulated over a 28-day cycle for zel (BT8009) (5 mg/m^2 QW) and BT5528 (5 mg/m^2 QW)
- Published PK parameters for enfortumab vedotin (EV), an MMAE-containing ADC, were obtained for comparison (1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle)[7]
- Three analytes were evaluated:
  - Conjugate: intact parent drug (zel [BT8009], BT5528, or EV)
  - Conjugated MMAE: MMAE attached to a bicyclic peptide or antibody (accounts for the number of MMAE molecules conjugated to each bicyclic peptide or antibody; **Figure 1**)
  - Unconjugated MMAE: MMAE released from the bicyclic peptide or antibody
- Conjugate exposures were expressed in terms of molar concentrations to facilitate qualitative comparison across various parent compounds from multiple clinical trials

FIGURE 1. ILLUSTRATION OF MMAE CONJUGATE FOR BTCs OR ADCs



MMAE-containing ADCs have approximately four MMAE molecules conjugated to each antibody.[7–10] Zel (BT8009) and BT5528 have one MMAE molecule conjugated to each bicyclic peptide.[2,4]

Safety

- Incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) were tabulated for zel (BT8009) and BT5528
- AEs of interest were defined by Standardised MedDRA® Query (SMQ) [broad] or preferred term per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

RESULTS

Pharmacokinetics

- **Figures 2 and 3** show concentration-time profiles for conjugate and unconjugated MMAE following EV (1.25 mg/kg)[7], zel (BT8009) (5 mg/m^2), and BT5528 (5 mg/m^2) administration
  - Although unconjugated MMAE disposition is generally similar following zel (BT8009)/BT5528 and EV administration, peak concentrations are achieved earlier for zel (BT8009)/BT5528 (**Figures 2 and 3**)
  - Zel (BT8009)/BT5528 half-life is substantially shorter than that of EV (<1 hour vs 3.6 days[7]), resulting in extensive elimination of conjugate within hours of dose administration, rather than weeks
  - MMAE half-life is also shorter following zel (BT8009)/BT5528 administration relative to EV (1.9 days vs 2.6 days[7]), potentially due to a slower rate of MMAE release from the ADC
- Relative to EV, zel (BT8009) and BT5528 achieve similar unconjugated MMAE AUCs over a 28-day cycle (85 ng*day/mL vs 92–106 ng*day/mL, **Table 1**) despite lower conjugate AUCs (724 nM*day vs 36.5–37.9 nM*day[7])
  - Conjugated MMAE AUC was substantially higher for EV relative to zel (BT8009)/BT5528 (1974 ng*day/mL vs 26.2–27.2 ng*day/mL)
- Relative to EV, zel (BT8009) and BT5528 maximum concentration (C_{max}) values were similar for conjugate (184 nM vs 149–178 nM), substantially lower for conjugated MMAE (503 ng/mL vs 107–128 ng/mL), and higher for unconjugated MMAE (5.5 ng/mL vs 16.1–16.8 ng/mL) (**Table 1**)

FIGURE 2. CONCENTRATION-TIME PROFILES OF A) ZEL (BT8009) CONJUGATE (LEFT) AND UNCONJUGATED MMAE (RIGHT) AND B) EV CONJUGATE (LEFT) AND UNCONJUGATED MMAE (RIGHT)[11]

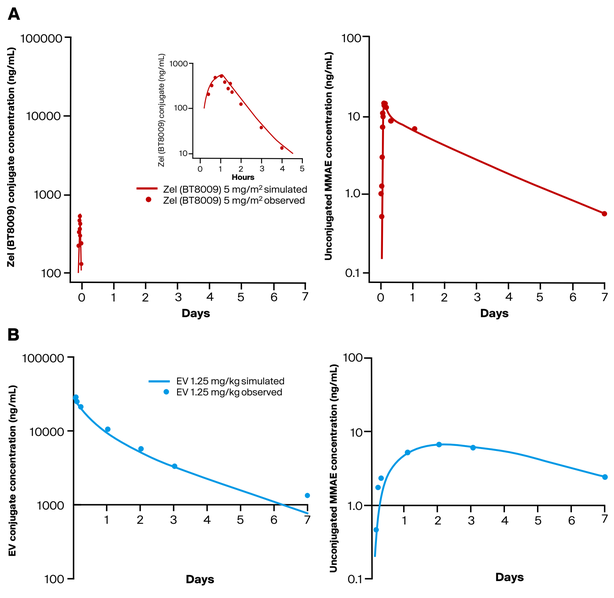


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TABLE 1. COMPARISON OF MEAN EXPOSURES FOR ZEL (BT8009), BT5528, AND EV

Analyte		Zel (BT8009)	BT5528	EV
Dosing regimen		5 mg/m^2 QW of a 28-day cycle		1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle
PK parameters by analyte				
Conjugate (parent drug)	Cycle 1 AUC (nM*day)	36.5	37.9	724[7]
	C_{max} (nM)	149	178	184[7]
Conjugated MMAE	Cycle 1 AUC (ng*day/mL)	26.2	27.2	1974
	C_{max} (ng/mL)	107	128	503
Unconjugated MMAE	Cycle 1 AUC (ng*day/mL)	106	92	85[7]
	C_{max} (ng/mL)	16.1	16.8	5.5[7]

FIGURE 3. ZEL (BT8009) AND BT5528 CONCENTRATION-TIME PROFILES OF CONJUGATE (TOP) AND UNCONJUGATED MMAE (BOTTOM)

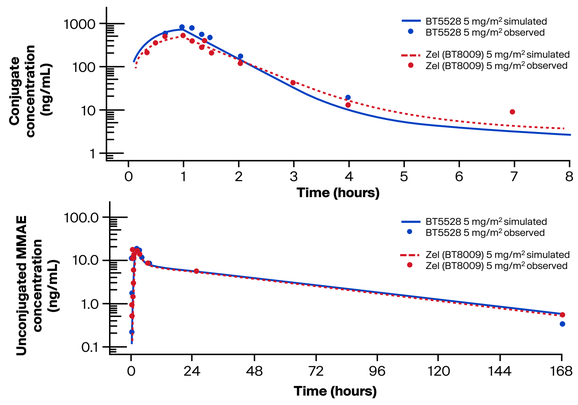

TABLE 2. SAFETY SUMMARY FOR ZEL (BT8009) AND BT5528

Event type, n (%)	Zel (BT8009) 5 mg/m^2 QW N=149	BT5528 6.5 mg/m^2 Q2W N=74
TEAEs overall	140 (94)	71 (96)
TEAEs Grade ≥3	81 (54)	36 (49)
TRAEs	125 (84)	67 (91)
TRAEs Grade ≥3	46 (31)	16 (22)
Any TESAE	50 (34)	19 (26)
BTC®-related TESAE	21 (14)	6 (8)
TEAEs leading to BTC dose modification	88 (59)	NA
TEAEs leading to BTC dose reduction	33 (22)	2 (3)
TEAEs leading to BTC dose rate reduction	1 (1)	1 (1)
TEAEs leading to BTC dose interruption	75 (50)	16 (22)
TEAEs leading to BTC dose withdrawn	5 (3)	2 (3)

Safety profile

- Safety data from all patients dosed at Cycle 1 Day 1 with zel (BT8009) 5 mg/m2 QW monotherapy (data as of 22 Mar 2024) and with BT5528 6.5 mg/m2 Q2W monotherapy (data as of 14 Mar 2024) are presented in **Table 2** and **Table 3** and summarized below:
  - Zel (BT8009)-related AEs occurred in 84% of patients; 31% were Grade ≥3 (**Table 2**). The most common any grade zel (BT8009)-related AEs (≥15% of patients) were nausea (33%), fatigue (30%), pyrexia (21%), diarrhea (20%), decreased appetite (18%), alopecia (17%), anemia (17%), and asthenia (17%)
  - BT5528-related AEs occurred in 91% of patients, of which 22% were Grade ≥3 (**Table 2**). The most common any grade BT5528-related AEs (≥15% of patients) were nausea (50%), fatigue (37%), diarrhea (31%), anemia (20%), decreased appetite (20%), pyrexia (18%), vomiting (18%), and alopecia (16%)
  - TRAEs of interest occurred with relatively low frequency and severity with both BTCs (**Table 3**)

TABLE 3. ZEL (BT8009) AND BT5528 TRAEs OF INTEREST

TRAE, n (%)	Zel (BT8009) 5 mg/m^2 QW N=149		BT5528 6.5 mg/m^2 Q2W N=74	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Peripheral neuropathy[a]	42 (28)	1 (1)	14 (19)	0
Skin reactions[b]	20 (13)	0	NA	NA
Neutropenia	17 (11)	9 (6)	6 (8)	2 (3)
Ocular disorders[c]	10 (7)	0	2 (3)	0
Hyperglycemia	7 (5)	2 (1)	3 (4)	1 (1)

[a]Peripheral neuropathy SMQ [broad] used. [b]All preferred terms defined in Skin and Subcutaneous Tissue SOC, excluding alopecia, and Severe Cutaneous Adverse Reaction MedDRA SMQ [broad] used. [c]Preferred terms defined in Eye Disorder SOC used.

CONCLUSION

- Preliminary data show substantial differences between BTC® and ADC PK profiles, with BTCs exhibiting rapid elimination of conjugate, substantially reduced conjugated MMAE exposures, comparable unconjugated MMAE AUC, and elevated unconjugated MMAE C_{max}
- Few Grade ≥3 TRAEs of interest were reported and were consistent with known MMAE-associated toxicity[12]
- The promising safety and tolerability profile, particularly in TRAEs of interest observed for BTCs, may be the result of the distinct PK, selectivity, and specificity of Bicycle® peptides
- These data highlight the potential value of BTCs as a platform for developing therapies against advanced malignancies

ABBREVIATIONS

ADCs, antibody-drug conjugates; AE, adverse event; AUC, area under the concentration curve; BTCs, Bicycle Toxin Conjugates®; C_{max}, maximum concentration; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; NA, not applicable; PK, pharmacokinetics; Q2W, every 2 weeks; QW, weekly; RP2D, recommended phase 2 dose; SMQ, Standardised MedDRA® Query; SOC, System Organ Class; TEAE, treatment-emergent AE; TESAE, treatment-emergent serious AE; TRAE, treatment-related AE; zel, zelenectide pevedotin.

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