No DDI Between Bemnifosbuvir/Ruzasvir and Bictegravir/Emtricitabine/Tenofovir Alafenamide

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WED-279

INTRODUCTION

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the hepatitis C virus (HCV) NS5B polymerase and NS5A protein, respectively[1,2]
- The combination of BEM 550 mg/RZR 180 mg once daily (QD) is under Phase 3 clinical development for the treatment of chronic HCV[3,4]
- B/FTC/TAF is a three-drug fixed-dose combination of bictegravir (B), an HIV-1 integrase strand transfer inhibitor, and the nucleosides emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 reverse transcriptase inhibitors[5]
- A Phase 1, open-label, multiple-dose study was conducted in healthy participants to evaluate the pharmacokinetic (PK) drug–drug interaction (DDI) between BEM/RZR and co-formulated antiretroviral B/FTC/TAF (NCT06356194)

METHODS

Study design

- 28 eligible healthy participants were enrolled and assigned to two groups according to a multiple-dose, three-period partial crossover design **(Figure 1)**
- Dosing occurred on an empty stomach and serial PK samples were obtained over 24 hours
- Plasma samples were quantitated for all study drugs/metabolites using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methodologies
- Potential PK DDIs were evaluated using geometric mean ratio (GMR) with 90% confidence interval (CI) for maximum plasma concentration (C_{max}), trough concentration (C_τ), and area under the concentration–time curve (AUC_T or AUC_τ) without (reference) and with the other drug
- Safety assessments included adverse events (AEs), vital signs, electrocardiograms (ECGs), and standard safety laboratory tests

Figure 1. Treatment schedule

Group 1

	Period 1	Period 2	Period 3
Group 1 (n=14)	**Days 1–7** 550 mg/180 mg BEM/RZR QD	**Days 8–17** 550 mg/180 mg BEM/RZR QD + 50 mg/200 mg/25 mg B/FTC/TAF QD	**Days 18–24** 50 mg/200 mg/25 mg B/FTC/TAF QD

Group 2

	Period 1	Period 2	Period 3
Group 2 (n=14)	**Days 1–10** 50 mg/200 mg/25 mg B/FTC/TAF QD	**Days 11–17** 550 mg/180 mg BEM/RZR QD + 50 mg/200 mg/25 mg B/FTC/TAF QD	**Days 18–24** 550 mg/180 mg BEM/RZR QD

RESULTS

Subject disposition and baseline characteristics

- 27/28 (96%) participants completed the study per protocol
- All 28 participants received ≥1 dose of study drug, had ≥1 post-dose PK sample evaluated and were therefore included in the PK and safety analyses
  - One participant withdrew consent before Period 2 and so is only included in the PK analysis for BEM/RZR alone
- Participants were generally well balanced across both groups **(Table 1)**

Table 1. Baseline demographic characteristics

Characteristic	Group 1 (n=14)	Group 2 (n=14)	Overall (N=28)
Mean age, years (range)	41.5 (23–55)	39.8 (23–53)	40.6 (23–55)
Male sex, n (%)	9 (64.3)	8 (57.1)	17 (60.7)
Race, n (%)			
Asian	1 (7.1)	0	1 (3.6)
Black or African American	1 (7.1)	1 (7.1)	2 (7.1)
White	12 (85.7)	13 (92.9)	25 (89.3)
Ethnicity, n (%)			
Hispanic/Latino	2 (14.3)	4 (28.6)	6 (21.4)
Non-Hispanic/Latino	12 (85.7)	10 (71.4)	22 (78.6)
Mean BMI, kg/m^2 (range)	24.9 (20.6–29.8)	25.2 (21.2–28.9)	25.0 (20.6–29.8)

BMI, body mass index.

Safety/tolerability evaluation

- BEM/RZR and B/FTC/TAF regimens were well tolerated in healthy participants when administered alone and in combination
- Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity. No serious AEs were reported and no participants discontinued due to a TEAE
- The most commonly reported TEAEs were constipation, procedural dizziness, and headache **(Table 2)**
- Drug-related TEAEs were infrequent
- There were no clinically significant changes in vital signs, ECG or laboratory parameters

Table 2. Summary of TEAEs according to treatment received

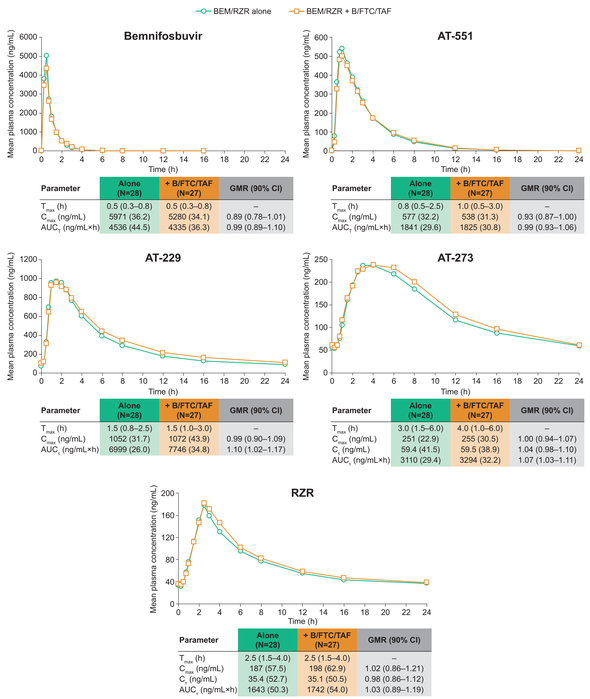
Parameter, n (%)	BEM/RZR (N=28)	BEM/RZR + B/FTC/TAF (N=28)	B/FTC/TAF (N=27)	Overall (N=28)
Participants with ≥1 drug-related TEAE*	2 (7.1)	0	1 (3.7)	3 (10.7)
TEAEs reported by ≥2 participants				
Constipation	0	1 (3.6)	3 (11.1)	4 (14.3)
Procedural dizziness	2 (7.1)	0	0	2 (7.1)
Headache	1 (3.6)	1 (3.6)	1 (3.7)	3 (10.7)

Percentages are based on the number of participants in the safety population in each treatment group.
*TEAE that was reported as 'Reasonable possibility'.

DDI evaluation

- Plasma concentration–time profiles for BEM, its metabolites AT-551 (L-alanyl intermediate), AT-229 (nucleoside metabolite) and AT-273 (plasma surrogate of the intracellular active triphosphate), and RZR, alone and in the presence of co-administered B/FTC/TAF, with summary PK results and comparative statistics, are presented in **Figure 2**
  - The plasma PK of BEM, its metabolites, and RZR were not significantly affected by B/FTC/TAF coadministration
- Plasma concentration–time profiles for bictegravir, FTC, tenofovir and TAF (the tenofovir prodrug), along with summary PK results and comparative statistics, are presented in **Figure 3**
  - The plasma PK of bictegravir and FTC were not significantly impacted by BEM/RZR coadministration
  - Peak and total exposure to TAF were increased by ~20% and ~50%, respectively, and the peak, trough, and total exposure to tenofovir were increased by ~45–50% by coadministration with BEM/RZR
- There were no significant changes in time to peak exposure (T_{max}) of the study drugs/metabolites when dosed alone or in the presence of the other drug

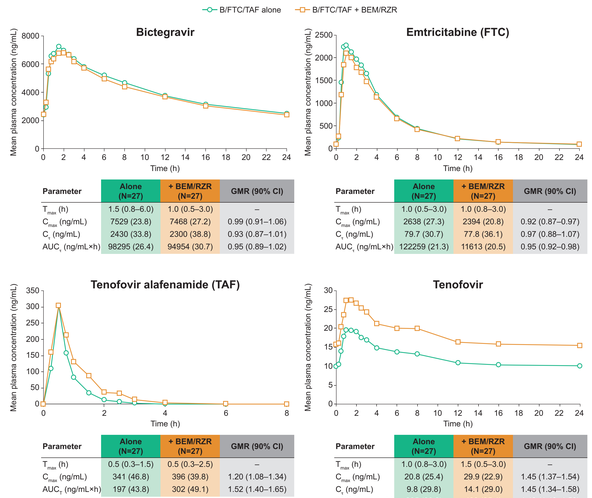
Figure 2. Effect of B/FTC/TAF on the plasma PK of BEM, its metabolites, and RZR



Parameter	Alone (N=28)	+ B/FTC/TAF (N=27)	GMR (90% CI)
Bemnifosbuvir			
T_{max} (h)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	–
C_{max} (ng/mL)	5971 (36.2)	5280 (34.1)	0.89 (0.78–1.01)
AUC_τ (ng/mL×h)	4536 (44.5)	4335 (36.3)	0.99 (0.89–1.10)
AT-551			
T_{max} (h)	0.8 (0.5–2.5)	1.0 (0.5–3.0)	–
C_{max} (ng/mL)	577 (32.2)	538 (31.3)	0.93 (0.87–1.00)
AUC_τ (ng/mL×h)	1841 (29.6)	1825 (30.8)	0.99 (0.93–1.06)
AT-229			
T_{max} (h)	1.5 (0.8–2.5)	1.5 (1.0–3.0)	–
C_{max} (ng/mL)	1052 (31.7)	1072 (43.9)	0.99 (0.90–1.09)
AUC, (ng/mL×h)	6999 (26.0)	7746 (34.8)	1.10 (1.02–1.17)
AT-273			
T_{max} (h)	3.0 (1.5–6.0)	4.0 (1.0–6.0)	–
C_{max} (ng/mL)	251 (22.9)	255 (30.5)	1.00 (0.94–1.07)
C_τ (ng/mL)	59.4 (41.5)	59.5 (38.9)	1.04 (0.98–1.10)
AUC_τ (ng/mL×h)	3110 (29.4)	3294 (32.2)	1.07 (1.03–1.11)
RZR			
T_{max} (h)	2.5 (1.5–4.0)	2.5 (1.5–4.0)	–
C_{max} (ng/mL)	187 (57.5)	198 (62.9)	1.02 (0.86–1.21)
C_τ (ng/mL)	35.4 (52.7)	35.1 (50.5)	0.98 (0.86–1.12)
AUC_τ (ng/mL×h)	1643 (50.3)	1742 (54.0)	1.03 (0.89–1.19)

Parameters are shown as mean (% coefficient of variation [CV]), except for T_{max} where median (range) are presented.

Figure 3. Effect of BEM + RZR on the plasma PK of bictegravir, FTC, TAF, and tenofovir



Parameter	Alone (N=27)	+ BEM/RZR (N=27)	GMR (90% CI)
Bictegravir			
T_{max} (h)	1.5 (0.8–6.0)	1.0 (0.5–3.0)	–
C_{max} (ng/mL)	7529 (23.8)	7468 (27.2)	0.99 (0.91–1.06)
C_τ (ng/mL)	2430 (33.8)	2300 (38.8)	0.93 (0.87–1.01)
AUC_τ (ng/mL×h)	98295 (26.4)	94954 (30.7)	0.95 (0.89–1.02)
Emtricitabine (FTC)			
T_{max} (h)	1.0 (0.5–3.0)	1.0 (0.8–3.0)	–
C_{max} (ng/mL)	2638 (27.3)	2394 (20.8)	0.92 (0.87–0.97)
C_τ (ng/mL)	79.7 (30.7)	77.8 (36.1)	0.97 (0.88–1.07)
AUC_τ (ng/mL×h)	122259 (21.3)	11613 (20.5)	0.95 (0.92–0.98)
Tenofovir alafenamide (TAF)			
T_{max} (h)	0.5 (0.3–1.5)	0.5 (0.3–2.5)	–
C_{max} (ng/mL)	341 (46.8)	396 (39.8)	1.20 (1.08–1.34)
AUC_τ (ng/mL×h)	197 (43.8)	302 (49.1)	1.52 (1.40–1.65)
Tenofovir			
T_{max} (h)	1.0 (0.8–3.0)	1.5 (0.5–3.0)	–
C_{max} (ng/mL)	20.8 (25.4)	29.9 (22.9)	1.45 (1.37–1.54)
C_τ (ng/mL)	9.8 (29.8)	14.1 (29.0)	1.45 (1.34–1.58)
AUC_τ (ng/mL×h)	295 (26.2)	439 (25.4)	1.49 (1.40–1.58)

Parameters are shown as mean (%CV), except for T_{max} where median (range) are presented.

CONCLUSIONS

- BEM/RZR and B/FTC/TAF, alone and coadministered, were safe and well tolerated in healthy participants
- The PK of BEM/RZR were not affected by coadministration with B/FTC/TAF
- The PK of bictegravir and emtricitabine were not affected by coadministration with BEM/RZR
- Peak, trough, and total exposure to TAF and tenofovir were increased by up to ~50% upon coadministration with BEM/RZR, which is deemed not clinically meaningful
- These results indicate a lack of clinically relevant DDI between BEM/RZR and B/FTC/TAF, supporting the enrollment of HCV/HIV-coinfected participants receiving these therapies in clinical trials

References

1. Berliba E, et al. Antimicrob Agents Chemother 2019;63:e01201–19
2. Asante-Appiah E, et al. Antimicrob Agents Chemother 2018;62:e01280–18
3. Jucov A, et al. EASL 2024; Abstract THU-382 and poster presentation
4. Good SS, et al. Antiviral Res 2025;237:106137
5. BIKTARVY® Prescribing Information. Gilead Sciences, Inc. (accessed March 2025)

Acknowledgments

This study was funded by Atea Pharmaceuticals (Boston, MA, USA). Medical writing and design support were provided by Obsidian Healthcare Group (London, UK) and were funded by Atea Pharmaceuticals.

Disclosures

XJZ, MM, SL, KP, BB, AH, and JH are employees of and may own stock in Atea Pharmaceuticals Inc., Boston, USA; GM, principal investigator of the study, is an employee of Altasciences, Quebec, Canada, which was contracted to perform the Phase 1 study.

Poster presented at The European Association for the Study of the Liver (EASL) Congress, May 7–10 2025, Amsterdam, The Netherlands.