Proton-pump inhibitor omeprazole did not affect the plasma pharmacokinetics of bemnifosbuvir and ruzasvir fixed-dose combination in healthy participants

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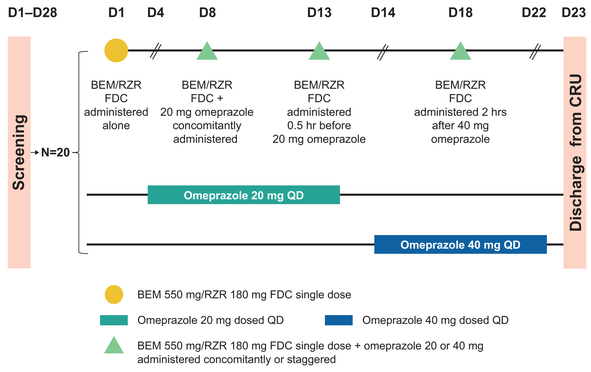
INTRODUCTION

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are direct-acting antivirals (DAAs), which are potent pangenotypic inhibitors of the hepatitis C virus (HCV) NS5B polymerase and NS5A protein, respectively[1,2]
- A fixed-dose combination (FDC) of BEM and RZR for the treatment of chronic HCV is currently in Phase 3 development[3,4]
- Proton-pump inhibitors such as omeprazole, are commonly used medications among HCV patients, which often reduce the solubility of DAAs, decreasing DAA absorption/bioavailability, and negatively impacting efficacy. Hence, it is crucial to assess pH-dependent drug–drug interaction (DDI) potential of omeprazole on the BEM/RZR FDC[5]
- We conducted a Phase 1, single center, open-label, fixed-sequence study to assess the effect of multiple doses of omeprazole on the single-dose pharmacokinetics (PK) of the BEM/RZR FDC in healthy adult participants under fasting conditions (NCT07007806)[6]
  - We also assessed the effect of a single dose of the BEM/RZR FDC on the PK of omeprazole, as well as the tolerability of the BEM/RZR FDC when administered alone vs concomitantly with omeprazole

METHODS

- **Figure 1** depicts the study design
  - A total of 20 healthy participants were enrolled
  - All participants received a single dose of BEM 550 mg/RZR 180 mg as 2 × FDC tablets on Day 1
  - Participants received omeprazole 20 mg once daily (QD) from Days 4–13 and 40 mg QD from Days 14–22
  - Participants received single doses of BEM/RZR FDC concomitantly with omeprazole (on Day 8), 0.5 hour before omeprazole (on Day 13), and 2 hours after omeprazole (on Day 18)
  - All dosing occurred under fasting conditions
- Intensive PK sampling was performed over 120 hours and plasma levels of BEM (and metabolites including AT-273, circulating surrogate of the intracellular active triphosphate metabolite of BEM) and RZR were quantitated using validated bioanalytical methods
- PK parameters reported are: maximum observed concentration (C_{max}), area under the concentration time curve extrapolated to infinity (AUC_{∞}), and area under the concentration time curve over the dosing interval at steady-state (AUC_{τ})
- Adverse event (AE) monitoring, clinical laboratory parameters, vital signs and electrocardiograms were assessed to evaluate safety

Figure 1. Study design



CRU, clinical research unit; D, day; FDC, fixed-dose combination; QD, once daily.
All dosing occurred under fasting conditions with 240 mL water.

RESULTS

- All 20 participants who received at least 1 dose of the study drug, and had at least 1 evaluable PK parameter, were included in the safety and PK analyses

Table 1. Participant demographics

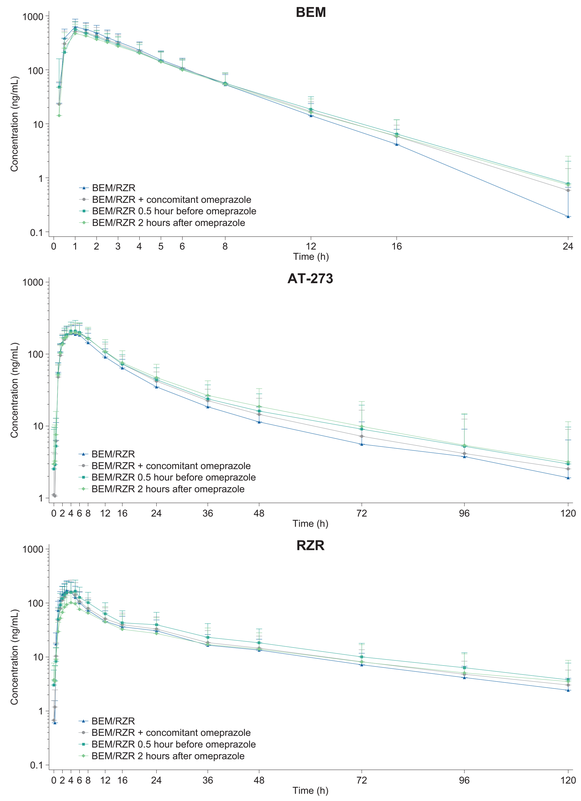
Characteristic	Overall (N=20)
Mean age, years (range)	40.5 (24–55)
Sex, n (%)	
Male	11 (55.0)
Female	9 (45.0)
Race, n (%)	
Asian	1 (5.0)
Black/African American	2 (10.0)
White	17 (85.0)
Ethnicity, n (%)	
Hispanic/Latino	9 (45.0)
Not Hispanic or Latino	11 (55.0)
Mean BMI, kg/m^2 (SD)	25.3 (2.8)

BMI, body mass index; N, number of participants in population; n, number of participants in sample; SD, standard deviation.

Effect of omeprazole on the PK of a single dose of BEM/RZR FDC

- The mean (+ standard deviation [SD]) plasma concentration–time profiles of BEM and its metabolite AT-273, and RZR, following a single dose administration of BEM 550 mg/RZR 180 mg FDC with or without the administration of omeprazole, respectively, are presented in **Figure 2**

Figure 2. Mean (+ SD) plasma concentration-time profiles of BEM, AT-273, and RZR following single dose administration of BEM/RZR FDC with or without omeprazole



Note: X-axis for BEM has been truncated to the last observable data point.

- The statistical analysis results for BEM, AT-273, and RZR following a single dose administration of BEM 550 mg/RZR 180 mg FDC concomitantly, 0.5 hour before, or 2 hours after the administration of omeprazole are presented in **Table 2**
- Concomitant administration of BEM/RZR FDC with omeprazole 20 mg did not markedly affect the plasma exposure to BEM, AT-273 or RZR
  - Changes in C_{max} and AUC_{∞} were minimal (within ±15%)
- Similarly, administration of BEM/RZR FDC 0.5 hour before did not markedly affect the plasma exposure to BEM, AT-273 or RZR
  - Changes in C_{max} and AUC_{∞} were minimal, mostly within ±15%, except for the AUC_{∞} of RZR which was increased by approximately 30%
- Administration of BEM/RZR FDC 2 hours after a high dose of omeprazole 40 mg
  - Slightly reduced the C_{max} and AUC_{∞} of BEM by approximately 24% and 17%, respectively, without affecting the plasma exposure to AT-273 (increased by up to approximately 15%)
  - Reduced the C_{max} of RZR by ~37% without markedly impacting its AUC_{∞} (decreased by <15%)
  - Changes in the AUC_{∞} of BEM, AT-273, and RZR were within 20%
- The median T_{max} of BEM were consistent regardless of administration of omeprazole

Table 2. Statistical analysis summary of BEM, AT-273, and RZR following administration of BEM/RZR FDC concomitantly, 0.5 hour before, and 2 hours after omeprazole, under fasted conditions

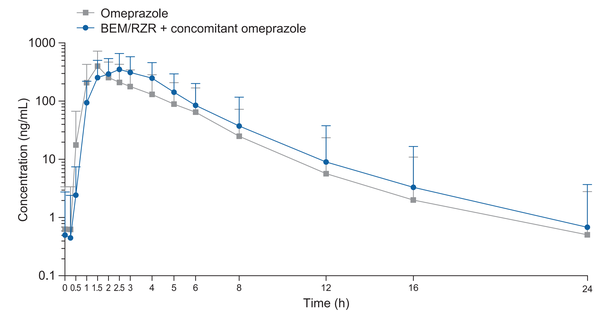
Parameter	Analyte	Geometric means (N=20)		GMR (90% CI)	CV (%)
		BEM/RZR + concomitant omeprazole	BEM/RZR		
Concomitant administration of BEM/RZR FDC and omeprazole					
C_{max} (ng/mL)	BEM	3340	3756	88.9 (74.2–106.6)	35.2
	AT-273	207	195	106.2 (96.9–116.3)	17.4
	RZR	143	152	94.1 (72.1–122.9)	53.9
AUC_{∞} (h*ng/mL)	BEM	2958	3247	91.1 (79.6–104.2)	25.9
	AT-273	3566	3157	112.9 (105.0–121.5)	13.9
	RZR	2275	2084	109.2 (83.7–142.4)	53.6
Administration of BEM/RZR FDC 0.5 hour before omeprazole					
		BEM/RZR 0.5 hour before omeprazole	BEM/RZR		
C_{max} (ng/mL)	BEM	3211	3756	85.5 (71.4–102.5)	35.2
	AT-273	212	195	108.6 (99.1–119.0)	17.4
	RZR	155	152	101.9 (78.0–133.1)	53.9
AUC_{∞} (h*ng/mL)	BEM	2958	3247	91.1 (79.6–104.2)	25.9
	AT-273	3594	3157	113.8 (105.8–122.4)	13.9
	RZR	2672	2084	128.3 (98.3–167.3)	53.6
Administration of BEM/RZR FDC 2 hours after omeprazole					
		BEM/RZR 2 hours after omeprazole	BEM/RZR		
C_{max} (ng/mL)	BEM	2871	3756	76.4 (63.8–91.6)	35.2
	AT-273	201	195	102.9 (94.0–112.8)	17.4
	RZR	97	152	63.6 (48.7–83.1)	53.9
AUC_{∞} (h*ng/mL)	BEM	2702	3247	83.2 (72.7–95.2)	25.9
	AT-273	3605	3157	114.2 (106.1–122.8)	13.9
	RZR	1800	2084	86.4 (66.2–112.7)	53.6

AUC_{∞}, area under the curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FDC, fixed-dose combination; GMR, geometric mean ratio.

Effects of a single dose of BEM/RZR FDC on the PK of omeprazole

- Mean concentration–time profiles of omeprazole following daily administration of omeprazole with or without the administration of BEM 550 mg/RZR 180 mg as 2 × FDC tablets are presented in **Figure 3**
- Concomitant administration of BEM/RZR FDC and omeprazole 20 mg did not meaningfully affect the C_{max} of omeprazole (increased by <3%), while increasing its AUC_{τ} by approximately 27%

Figure 3. Mean (+ SD) plasma concentration-time profiles of omeprazole following administration of omeprazole with or without BEM/RZR FDC under fasting conditions



Safety and tolerability

- Overall, 4/20 participants (20%) reported treatment-emergent adverse events (TEAEs). The only AEs reported were headache or nausea; all were mild
- One participant experienced headache after receiving 20 mg omeprazole alone (between Days 4–7); three participants experienced headache and/or nausea after receiving 20 mg omeprazole and BEM/RZR concomitantly (between Days 8–12); no other TEAEs were reported in other periods
- No TEAEs were considered related to either drug alone
- No serious AEs leading to study discontinuation or deaths were reported
- No clinically significant changes in vital signs,12-lead ECGs, physical examinations, or laboratory values were observed during the study

CONCLUSIONS

- BEM/RZR FDC was generally safe and well tolerated when administered alone or concomitantly with omeprazole
- Omeprazole 20 mg QD administered simultaneously or staggered with BEM/RZR FDC essentially did not affect the plasma PK of BEM, its metabolite AT-273, or RZR
- Omeprazole 40 mg QD, a higher staggered dose representing potentially a worst-case DDI scenario, only slightly decreased the plasma exposure to BEM and RZR without affecting AT-273
- Concomitant administration of BEM/RZR FDC and omeprazole had minimal effect on the PK profile of omeprazole
- Study results support unrestrictive co-administration of BEM/RZR FDC with omeprazole 20 or 40 mg in individuals infected with HCV

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Disclosures

XJZ, MM, KP, BB, SL, DL, MAH, and JH are employees of and may own stock in Atea Pharmaceuticals. BS is an employee of Altasciences, which was contracted to support the study execution and data analysis.

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