Bemnifosbuvir and Ruzasvir Provided as a Fixed-Dose Combination Demonstrates High Relative Bioavailability to Their Individual Formulations and Can Be Dosed With No Regard to Food

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INTRODUCTION

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent pangenotypic inhibitors of the HCV NS5B polymerase and NS5A protein, respectively[1,2]
- A fixed-dose combination (FDC) of BEM and RZR (550 mg BEM and 180 mg RZR as two FDC tablets with each tablet containing 275 mg BEM and 90 mg RZR) for the treatment of chronic HCV is currently in Phase 3 development[3,4]
- We conducted a Phase 1 study to assess the relative bioavailability (rBA) of the BEM/RZR FDC compared with concomitant administration of BEM and RZR in their individual dosage forms, in healthy adult participants (NCT06204679)
  - Considering the potential effect of food and acid-reducing agents on oral drug bioavailability, we also assessed the effect of food or famotidine (FAM, a histamine H2-receptor antagonist[5]) on the pharmacokinetics (PK) of the BEM/RZR FDC
  - The study also assessed the safety and tolerability of BEM and RZR

METHODS

Study design

- **Figure 1** depicts the study design, which included 24 healthy participants who initially received concomitant administration of a single dose of BEM 550 mg (as 2 × 275 mg tablets) and RZR 180 mg (as 2 × 90 mg capsules) in their individual dosage forms under fasting conditions, as reference
  - The participants then received a single dose of BEM/RZR as 2 × FDC tablets under fasting and fed (with a high-fat, high-calorie [HFHC] meal) conditions according to a crossover design
- The participants also received 2 doses of 20 mg FAM ~12 hours apart, with BEM/RZR FDC taken simultaneously (N=12) or 2 hours after (N=12) the second dose of FAM under fasted conditions
- Intensive PK sampling of blood samples was performed over 144 hours, and plasma concentrations of BEM (and its metabolites) and RZR were quantitated using validated bioanalytical methodologies

Figure 1. Study design

BEM and RZR individual doses taken concomitantly (fasted)*	BEM/RZR FDC (fasted)	BEM/RZR FDC (fed with a HFHC meal)	2 FAM doses ~12 hours apart + BEM/RZR FDC (fasted) simultaneously with the second FAM dose
	BEM/RZR FDC (fed with a HFHC meal)	BEM/RZR FDC (fasted)	2 FAM doses ~12 hours apart + BEM/RZR FDC (fasted) 2 h after the second FAM dose

*Reference formulations.
Abbreviations: BEM, bemnifosbuvir; FAM, famotidine; FDC, fixed-dose combination; HFHC, high-fat, high-calorie; RZR, ruzasvir.

RESULTS

Baseline characteristics

Table 1. Baseline demographics

Characteristic	N=24
Mean age, years (range)	45 (25–65)
Male sex, n (%)	18 (75.0)
Race, n (%)	
White	11 (45.8)
Black/African-American	8 (33.3)
Asian	1 (4.2)
Other	4 (16.7)
Mean BMI, kg/m² (SD)	26.4 (2.5)

Abbreviations: BMI, body mass index; N, total number of participants; n, number of participants in a category; SD, standard deviation.

PK analysis

rBA of BEM/RZR FDC vs reference formulations under fasting conditions

- **Figure 2 and Figure 3** depict the mean (+standard deviation [SD]) plasma concentration–time profiles of BEM (and its guanosine metabolite AT-273, which is considered the plasma surrogate of the intracellular active triphosphate AT-9010) and RZR administered as BEM/RZR FDC vs reference formulations, respectively
- **Table 2** summarizes the statistical analysis results for BEM, AT-273, and RZR
- For both BEM and AT-273, the median T_{max} was similar between the BEM/RZR FDC and reference formulations, whereas the median T_{max} for RZR was 3.5 h for the BEM/RZR FDC and 2.5 h for the reference formulations
- Based on C_{max} and $AUC_{0-\infty}$, the BEM/RZR FDC exhibited a high rBA to the reference formulations (geometric mean ratio [GMR] ranging from ~78–114% for C_{max} and 87–113% for $AUC_{0-\infty}$)

Figure 2: Mean (+SD) plasma concentration–time profiles of BEM (A) and AT-273 (B) administered as BEM/RZR FDC vs reference formulations (under fasted conditions)

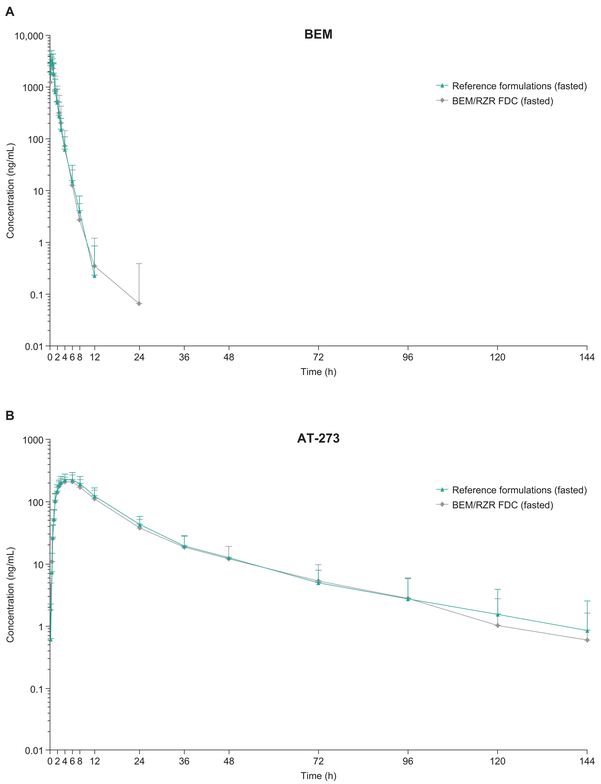

Figure 3. Mean (+SD) plasma concentration-time profiles of RZR administered as BEM/RZR FDC vs reference formulations (under fasted conditions)

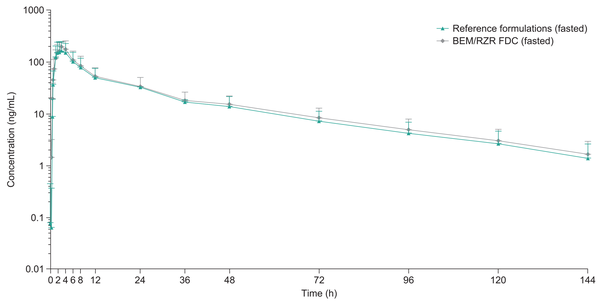

Table 2. rBA assessment: BEM/RZR FDC vs reference formulations

Parameter	Analyte	Geometric means (n)		GMR (90% CI)	CV (%)
		BEM/RZR FDC fasted	Reference formulation fasted		
C_{max} (ng/mL)	BEM	3057 (24)	3904 (22)	78.3 (63.8–96.2)	43.3
	AT-273	221 (24)	236 (22)	93.4 (83.3–104.6)	23.2
	RZR	173 (24)	152 (22)	114.1 (85.1–152.8)	64.5
$AUC_{0-\infty}$ (h*ng/mL)	BEM	2968 (23)	3421 (22)	87.0 (69.9–107.7)	45.2
	AT-273	3456 (23)	3884 (21)	89.0 (78.4–101.0)	25.4
	RZR	2628 (24)	2317 (21)	113.4 (86.3–149.1)	58.8

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration–time curve from time zero to infinity, representing total plasma exposure; CI, confidence interval; C_{max}, peak plasma exposure; FDC, fixed-dose combination; GMR, geometric mean ratio; CV, intraindividual coefficient of variation; n, number of participants in each category; RZR, ruzasvir.

Food effect on BEM/RZR FDC

- **Table 3** summarizes the statistical analysis results for BEM, AT-273, and RZR, when administered as the BEM/RZR FDC under fasted vs fed (HFHC meal) conditions
- The median T_{max} of BEM increased from 0.5 h (fasted) to 2 h (fed), and from 4 h (fasted) to 6 h (fed) for AT-273, whereas the median T_{max} for RZR remained unchanged
- A HFHC meal increased the total plasma exposure ($AUC_{0-\infty}$) of BEM, AT-273, and RZR when administered as BEM/RZR FDC by ~9%, 11%, and 38%, respectively

Table 3. Food-effect assessment: BEM/RZR FDC fed vs fasted

Parameter	Analyte	Geometric means (n)		GMR (90% CI)	CV (%)
		BEM/RZR FDC fed	BEM/RZR FDC fasted		
C_{max} (ng/mL)	BEM	1631 (24)	3057 (24)	53.4 (41.7–68.3)	54.4
	AT-273	246 (24)	221 (24)	111.4 (99.1–125.1)	24.4
	RZR	193 (24)	173 (24)	111.4 (89.2–139.1)	48.4
$AUC_{0-\infty}$ (h*ng/mL)	BEM	3222 (21)	2968 (23)	108.6 (88.4–133.4)	42.3
	AT-273	3838 (24)	3456 (23)	111.1 (98.5–125.2)	24.8
	RZR	3639 (24)	2628 (24)	138.5 (112.1–171.0)	45.8

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity, representing total plasma exposure; CI, confidence interval; C_{max}, peak plasma exposure; FDC, fixed-dose combination; GMR, geometric mean ratio; CV, intraindividual coefficient of variation; n, number of participants in each category; RZR, ruzasvir.

Effect of FAM on BEM/RZR FDC

- **Table 4** and **Table 5** summarize the statistical analysis results for BEM, AT-273, and RZR, when administered as the BEM/RZR FDC alone vs co-administered simultaneously with or 2 h after the second dose of FAM, respectively
- The median T_{max} for BEM (0.5 h) and RZR (3.5–4 h) remained unchanged when administered as the BEM/RZR FDC alone vs either co-administered simultaneously with or 2 h after the second dose of FAM
  - The median T_{max} of AT-273 (4 h) was similar when dosed as BEM/RZR FDC alone or 2 h after the second dose of FAM, and was 6 h when co-administered simultaneously with FAM
- When the BEM/RZR FDC was dosed 2 h after, FAM had limited effect on BEM (<20%) and did not affect AT-273, but decreased the C_{max} and $AUC_{0-\infty}$ of RZR by ~45% and 40%, respectively
- In contrast, when dosed simultaneously with the BEM/RZR FDC, FAM did not affect the plasma exposure of BEM, AT-273, or RZR, with GMR ranging from ~90%–103%

Table 4. DDI assessment: BEM/RZR FDC + FAM simultaneously vs BEM/RZR FDC alone

Parameter	Analyte	Geometric means (n)		GMR (90% CI)	CV (%)
		BEM/RZR FDC + FAM	BEM/RZR FDC alone		
C_{max} (ng/mL)	BEM	2969 (12)	3057 (24)	97.1 (75.1–125.6)	17.6
	AT-273	215 (12)	221 (24)	97.3 (87.4–108.3)	15.9
	RZR	156 (12)	173 (24)	90.2 (70.4–115.8)	40.1
$AUC_{0-\infty}$ (h*ng/mL)	BEM	2824 (12)	2948 (23)	95.8 (81.4–112.8)	31.7
	AT-273	3502 (11)	3463 (23)	101.1 (91.6–111.6)	20.2
	RZR	2699 (12)	2628 (24)	102.7 (83.2–126.7)	40.6

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity, representing total plasma exposure; CI, confidence interval; C_{max}, peak plasma exposure; DDI, drug–drug interaction; FDC, fixed-dose combination; GMR, geometric mean ratio; CV, intraindividual coefficient of variation; n, number of participants in each category; RZR, ruzasvir.

Table 5. DDI assessment: BEM/RZR FDC 2 hours after the second dose of FAM vs BEM/RZR FDC alone

Parameter	Analyte	Geometric means (n)		GMR (90% CI)	CV (%)
		BEM/RZR FDC 2 hours after second FAM dose	BEM/RZR FDC alone		
C_{max} (ng/mL)	BEM	2696 (12)	3057 (24)	88.2 (70.8–110.0)	30.4
	AT-273	201 (12)	221 (24)	91.0 (83.3–99.5)	20.0
	RZR	95 (12)	173 (24)	55.0 (41.0–73.7)	39.2
$AUC_{0-\infty}$ (h*ng/mL)	BEM	2385 (12)	2964 (23)	81.0 (69.4–93.3)	36.7
	AT-273	3487 (12)	3470 (23)	100.6 (92.2–109.7)	23.8
	RZR	1578 (12)	2628 (24)	60.0 (45.2–79.9)	41.4

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration–time curve from time zero to infinity, representing total plasma exposure; CI, confidence interval; C_{max}, peak plasma exposure; CV, intraindividual coefficient of variation; DDI, drug–drug interaction; FAM, famotidine; FDC, fixed-dose combination; GMR, geometric mean ratio; n, number of participants in each category; RZR, ruzasvir.

Safety and tolerability

- Of the 24 participants who received the BEM/RZR FDC, 8 (33%) experienced an adverse event (AE). All were mild in intensity, with none resulting in study discontinuation. Mild nausea (n=2) was the only AE reported in more than 1 participant, with no patterns related to dosing with/without food or with FAM administration
- Two participants reported 3 drug-related AEs (nausea, headache, petechiae) following administration of FAM followed by the BEM/RZR FDC

CONCLUSIONS

- The BEM/RZR FDC had a high relative bioavailability, equivalent to BEM and RZR administered concomitantly in their individual reference dosage forms, and can be taken with or without food
- The BEM/RZR FDC can be co-administered simultaneously with FAM, an H2-blocker
- BEM/RZR FDC was well tolerated with or without food, or with FAM
- Study results supported the selection of the BEM/RZR FDC for ongoing and future clinical studies

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. NCT07037277. Available at: ClinicalTrials.gov. Accessed October 2025.
4. NCT06868264. Available at: ClinicalTrials.gov. Accessed October 2025.
5. US Food and Drug Administration. Evaluation of gastric pH-DDIs with ARAs: study design, data analysis, and clinical implications. Available at: FDA guidance on ARA DDIs. Accessed October 2025.

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Disclosures

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