Lack of pharmacokinetic drug–drug interaction between bemnifosbuvir and ruzasvir in healthy participants

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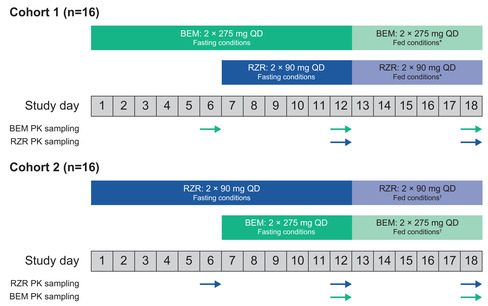
BACKGROUND

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pangenotypic inhibitors of the HCV NS5B polymerase and NS5A protein, respectively[1,2]
- Combinations of BEM with daclatasvir, an NS5A inhibitor, and RZR with uprifosbuvir, an experimental nucleotide NS5B inhibitor, were safe and well tolerated, and independently achieved high rates of sustained virologic response at 12 weeks in HCV-infected participants[3,4]
- *In vitro* studies demonstrate that BEM is approximately 10-fold more active vs sofosbuvir against laboratory strains and clinical isolates of HCV genotypes 1–5, and retains full activity against S282T, an amino acid substitution associated with sofosbuvir resistance[1,5]
- BEM and RZR exhibited synergistic anti-HCV activity *in vitro*[6]
- Cumulative data suggest that, in addition to having a low potential for drug–drug interactions (DDIs), combination BEM and RZR may be highly efficacious, with a shorter treatment duration, in a broad HCV patient population[6]
- Here we report results from a Phase 1 pharmacokinetic (PK) DDI study of BEM and RZR in healthy participants with food effect evaluation[7]

METHODS

- 32 eligible, healthy adult participants were enrolled and took the study drugs as specified in **Figure 1**
- Intensive PK sampling was performed over 24 hours (h) on Days 6, 12, and 18, and plasma concentrations of BEM and metabolites and RZR were quantitated using validated bioanalytical methodologies
- Metabolites of BEM for PK analysis include:
  - AT-511, the freeform base of BEM which forms after dissolution of BEM[1]
  - AT-551, the L-alanyl metabolite of AT-511 following hydrolysis[2,8]
  - AT-229 and AT-273, which are major circulating nucleoside metabolites (AT-273, the guanosine metabolite, is considered the surrogate of the intracellular active triphosphate of BEM)[1,8]
- DDIs were assessed by comparing PK results on Day 12 (combined) with Day 6 (alone), and food effect was assessed by comparing PK results on Day 18 (fed) with Day 12 (fasted)
- Safety assessments included adverse events (AEs), vital signs, physical examination, electrocardiograms (ECGs), and standard clinical laboratory tests

Figure 1. Study design



*Low-fat meal. †Moderate-fat meal.
QD, once daily.

RESULTS

Study population

- All 32 participants completed the study and were included in the PK and safety analysis populations
- Participants were generally matched across cohorts **(Table 1)**

Table 1. Demographics

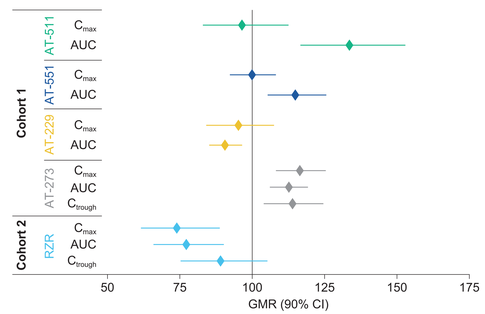
Characteristic	Cohort 1 n=16	Cohort 2 n=16	Total N=32
Mean age, years (SD, min–max)	40 (10.7, 23–55)	35 (11.6, 20–53)	37 (11.3, 20–55)
Female, n (%)	8 (50.0)	11 (68.8)	19 (59.4)
Race, n (%)			
White	15 (93.8)	13 (81.3)	28 (87.5)
Black or African American	1 (6.3)	3 (18.8)	4 (12.5)
Mean BMI, kg/m² (SD, min–max)	25 (3.3, 21–30)	26 (3.2, 21–31)	26 (3.2, 21–31)

BMI, body mass index; max, maximum; min, minimum; n, number; SD, standard deviation.

PK analysis: DDI

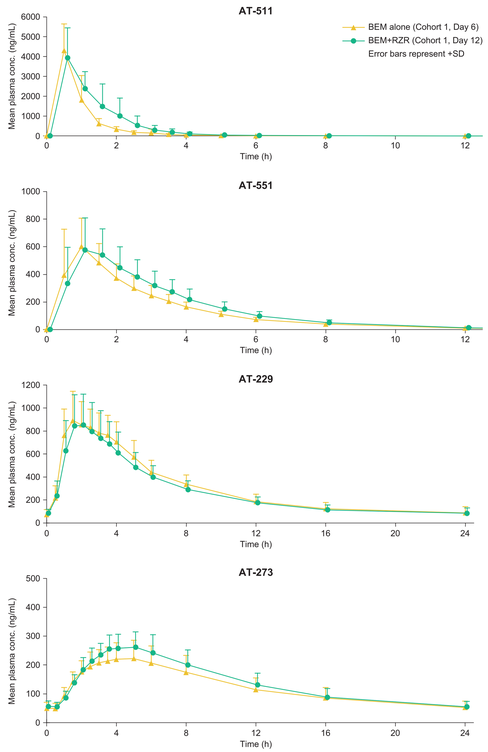
- Coadministered RZR did not significantly alter the plasma PK of BEM **(Figure 2; Figure 3)**
  - Total peak and/or trough exposures for AT-511, AT-551, AT-229, and AT-273, in the presence of RZR, were typically within 15% of when BEM was dosed alone

Figure 2. Effect of RZR on BEM PK (Cohort 1) and effect of BEM on RZR PK (Cohort 2)



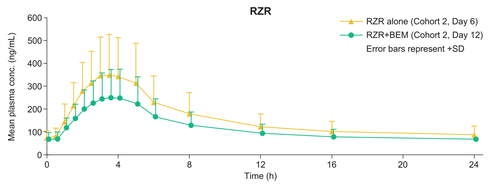
AUC, area under curve up to last quantifiable timepoint; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; GMR, geometric mean ratio.

Figure 3. Effect of RZR on BEM in Cohort 1



- Coadministered BEM did not meaningfully alter the plasma PK of RZR **(Figure 2; Figure 4)**
  - Coadministered BEM decreased the total and peak exposures of RZR by approximately 20–25%, while the trough exposure of RZR was minimally affected

Figure 4. Effect of BEM on RZR in Cohort 2



PK analysis: food effect

- When BEM and RZR were coadministered, a low- and moderate-fat meal did not significantly affect the plasma exposure of AT-273, while slightly increasing that of RZR **(Figure 5; Figure 6)**
- Attainment of peak exposure was generally delayed with food for AT-511, AT-551, and AT-229, but to a lesser extent for AT-273 and RZR **(Figure 5)**

Figure 5. Effect of a low-fat meal (A) and moderate-fat meal (B) on study drug PK

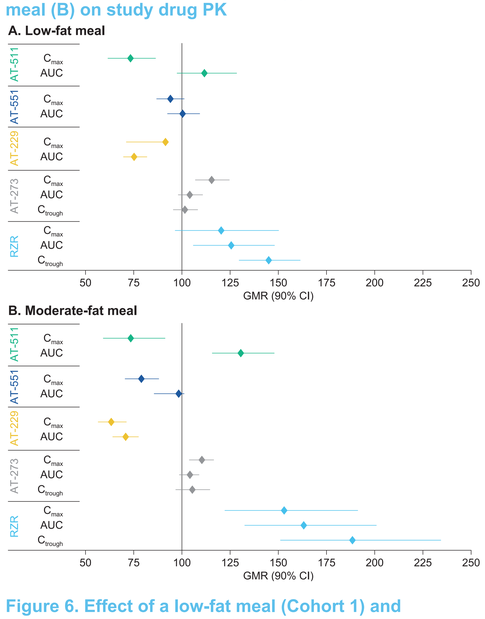


Figure 6. Effect of a low-fat meal (Cohort 1) and moderate-fat meal (Cohort 2) on BEM in the presence of RZR

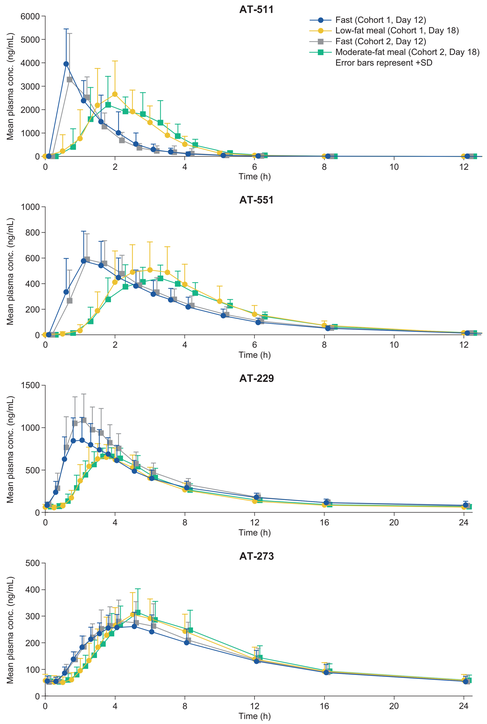
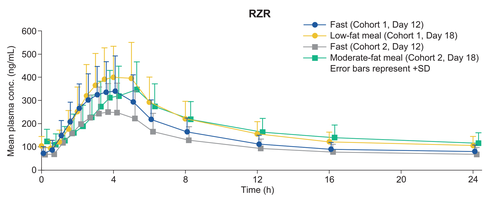


Figure 7. Effect of a low-fat meal (Cohort 1) and moderate-fat meal (Cohort 2) on RZR in the presence of BEM



Safety

- All treatment-emergent AEs (TEAEs) were non-serious. Nearly all TEAEs were mild (1/69 TEAEs was of moderate severity)
- No deaths or serious TEAEs were reported and no participants were withdrawn due to a TEAE
- No clinically significant laboratory abnormalities, physical examination, ECG, or vital sign measurements were observed

CONCLUSIONS

- Here we report the first clinical data for the coadministration of BEM and RZR
- The study drugs were well tolerated and plasma PK profiles were not substantially affected by food nor concomitant dosing, the latter indicating lack of DDI between BEM and RZR
- These data support the evaluation of the combination of these highly potent molecules for the treatment of HCV
- A phase 2 trial evaluating the combination of BEM and RZR administered once daily for 8 weeks in HCV-infected patients is ongoing[9]

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Acknowledgements

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Disclosures

Xiao-Jian Zhou, Maureen Montrond, Shannan Lynch, Keith Pietropaolo, Bruce Belanger, Arantxa Horga, and Janet Hammond are employees of and may own stock in Atea Pharmaceuticals, Boston, MA, USA.
Gaetano Morelli, principal investigator of the study, is an employee of Altasciences Company Inc, Montreal, Canada, which was contracted to perform this research.

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