# Bemnifosbuvir and ruzasvir administered as a fixed-dose combination has low potential to inhibit P-gp, BCRP or OATP1B1/3 mediated transport

FRI-636

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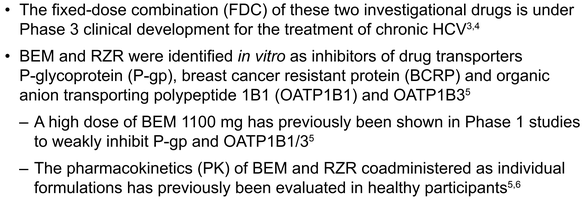
## INTRODUCTION

- 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 fixed-dose combination (FDC) of these two investigational drugs is under Phase 3 clinical development for the treatment of chronic HCV[3,4]
- BEM and RZR were identified *in vitro* as inhibitors of drug transporters P-glycoprotein (P-gp), breast cancer resistant protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3[5]
  - A high dose of BEM 1100 mg has previously been shown in Phase 1 studies to weakly inhibit P-gp and OATP1B1/3[5]
  - The pharmacokinetics (PK) of BEM and RZR coadministered as individual formulations has previously been evaluated in healthy participants[5,6]
- A Phase 1, open-label study in healthy participants was conducted to assess the effect of the BEM/RZR FDC on the PK of digoxin (DIG) and rosuvastatin (ROSU) as P-gp and BCRP/OATP1B1/1B3 index substrates, respectively (NCT06921941)[7]

## METHODS

- 38 eligible, healthy participants were enrolled into 2 groups to evaluate the effect of a single dose of BEM 550 mg/RZR 180 mg administered as 2 x FDC tablets on the plasma PK of a single dose of DIG 0.25 mg and ROSU 10 mg, respectively
- Participants were randomized according to a 3-period, 3-sequence crossover design and received in each period on an empty stomach the index substrate alone, with simultaneously administered BEM/RZR FDC or 2 hours ahead of BEM/RZR FDC **(Figure 1)**
- Serial plasma samples were collected prior to and over 72 hours post dosing in each period for both DIG and ROSU, and quantitated for DIG or ROSU concentrations using validated LC/MS-MS methodologies
- PK analyses were performed using non-compartmental approaches
- Drug–drug interactions (DDIs) were assessed by an analysis of variance (ANOVA) on the natural log-transformed PK parameters area under the concentration time curve extrapolated to infinity ($AUC_\infty$) and maximum observed concentration ($C_{max}$) of drug exposure with study day (treatment) as a fixed factor and participant as a random effect
- Safety assessments included adverse events (AEs), vital signs, physical examination, electrocardiograms (ECGs), and standard clinical laboratory tests

### Figure 1. Treatment schedules for the DIG and ROSU study groups




The washout was 14 days for Part 1 (DIG) and 7 days for Part 2 (ROSU).

## RESULTS

### Participant disposition and demographics

- 20 participants (Part 1 [DIG]) and 18 participants (Part 2 [ROSU]) received ≥1 dose of study drug and had ≥1 evaluable post-dose PK parameter result, and were therefore included in the safety and PK analyses
  - In Part 1 (DIG), 2 participants were prematurely discontinued based on physician's decision due to laboratory abnormalities (ALT/AST and potassium) and were replaced
  - In Part 2 (ROSU), 2 participants were prematurely discontinued (positive urine cotinine test and consent withdrawn) and were not replaced
- Thus, 18/20 (90%) participants and 16/18 (89%) participants completed Part 1 (DIG) and Part 2 (ROSU), respectively
- Participant demographics are presented in **Table 1**

### Table 1. Participant demographics

| Characteristic | Part 1 (DIG) (N=20) | Part 2 (ROSU) (N=18) |
|---|---|---|
| Mean age, years (range) | 41.4 (18–55) | 38.2 (20–54) |
| Male sex, n (%) | 11 (55.0) | 9 (50.0) |
| Female sex, n (%) | 9 (45.0) | 9 (50.0) |
| Race, n (%) | | |
| Asian | 1 (5.0) | 2 (11.1) |
| Black/African American | 2 (10.0) | 4 (22.2) |
| White | 14 (70.0) | 11 (61.1) |
| Other | 3 (15.0) | 1 (5.6) |
| Ethnicity, n (%) | | |
| Hispanic/Latino | 10 (50.0) | 5 (27.8) |
| Not Hispanic/Latino | 10 (50.0) | 13 (72.2) |
| Mean BMI, kg/m² (SD) | 25.4 (2.3) | 25.6 (3.0) |

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

### DDI evaluation

*Part 1 (DIG)*

- A single dose of BEM/RZR FDC administered simultaneously increased, transiently, the $C_{max}$ of DIG by 59%, with no effect on its overall exposure **(Tables 2 and 3)**
- When dosed staggered 2 hours later, BEM/RZR FDC did not affect the $C_{max}$ or $AUC_\infty$ of DIG **(Table 2, Figure 2)**
- Simultaneous or staggered dosing of BEM/RZR FDC did not affect the time of maximum observed concentration ($T_{max}$) and terminal elimination half-life ($T_{1/2}$) of DIG

### Table 2. Summary of statistical analysis of the effect of BEM/RZR FDC on the PK of DIG

| Treatment | GMR (90% CI) | |
|---|---|---|
| | $C_{max}$ | $AUC_\infty$ |
| Simultaneous DIG + BEM/RZR FDC | 1.59 (1.36–1.85) | 1.03 (94.4–1.13) |
| Staggered DIG + BEM/RZR FDC | 0.98 (0.84–1.15) | 1.09 (0.99–1.19) |

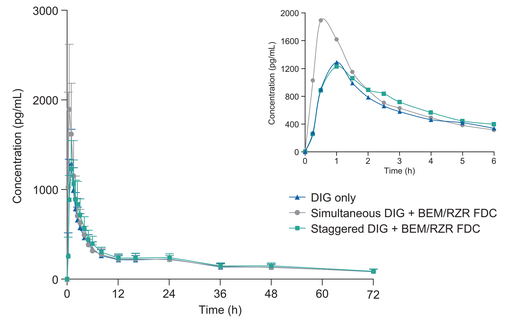
$AUC_\infty$, area under the concentration time curve extrapolated to infinity; CI, confidence interval; $C_{max}$, maximum observed concentration; FDC, fixed-dose combination; GMR, geometric mean ratio.

### Table 3. Summary of DIG PK parameters

| Treatment | $C_{max}$ (pg/mL) | $T_{max}$ (h) | $AUC_\infty$ (pg/mL×h) | $T_{1/2}$ (h) |
|---|---|---|---|---|
| DIG only | 1317 (30.3) | 1.01 (0.51–1.50) | 19591 (18.7) | 41.6 (20.7) |
| Simultaneous DIG + BEM/RZR FDC | 2142 (35.4) | 0.57 (0.33–1.50) | 20470 (24.1) | 39.6 (28.0) |
| Staggered DIG + BEM/RZR FDC | 1267 (23.5) | 1.00 (0.57–2.00) | 21486 (29.0) | 41.8 (44.2) |

$AUC_\infty$, area under the concentration time curve extrapolated to infinity; $C_{max}$, maximum observed concentration; FDC, fixed-dose combination; h, hour; $T_{max}$, time of maximum observed concentration; $T_{1/2}$, terminal elimination half-life.
$C_{max}$, $AUC_\infty$, and $T_{1/2}$ are represented as arithmetic mean (arithmetic CV%). $T_{max}$ is represented as median [minimum–maximum].

### Figure 2. Mean ± SD PK profiles of DIG following simultaneous or staggered dosing of BEM/RZR FDC




Insert shows mean PK profile (without SD) with truncated X/Y axis to better visualize the transient effect of BEM/RZR on the PK of DIG.

*Part 2 (ROSU)*

- A single dose of BEM/RZR FDC administered simultaneously increased the peak and total plasma exposure of ROSU by 79% and 40%, respectively **(Tables 4 and 5)**
- Staggered dosing of BEM/RZR FDC 2 hours later reduced these effects by approximately half, with a 34% and 22% increase in the peak and total exposure to ROSU, respectively **(Table 4, Figure 3)**
- Simultaneous or staggered BEM/RZR FDC did not affect the $T_{max}$ or $T_{1/2}$ of ROSU

### Table 4. Summary of statistical analysis of the effect of BEM/RZR FDC on the PK of ROSU

| Treatment | GMR (90% CI) | |
|---|---|---|
| | $C_{max}$ | $AUC_\infty$ |
| Simultaneous ROSU + BEM/RZR FDC | 1.79 (1.56–2.05) | 1.40 (1.25–1.57) |
| Staggered ROSU + BEM/RZR FDC | 1.34 (1.17–1.54) | 1.22 (1.08–1.38) |

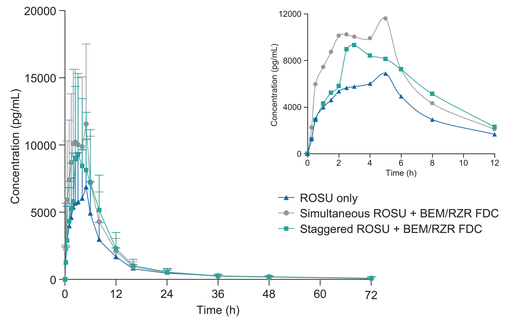
$AUC_\infty$, area under the concentration time curve extrapolated to infinity; CI, confidence interval; $C_{max}$, maximum observed concentration; FDC, fixed-dose combination; GMR, geometric mean ratio.

### Table 5. Summary of ROSU PK parameters

| Treatment | $C_{max}$ (pg/mL) | $T_{max}$ (h) | $AUC_\infty$ (pg/mL×h) | $T_{1/2}$ (h) |
|---|---|---|---|---|
| ROSU only | 7009 (52.8) | 5.00 (1.07–5.01) | 73481 (38.0) | 23.4 (67.3) |
| Simultaneous ROSU + BEM/RZR FDC | 12130 (49.5) | 5.00 (0.25–5.02) | 103044 (44.1) | 22.6 (74.1) |
| Staggered ROSU + BEM/RZR FDC | 10315 (57.6) | 3.00 (2.50–6.01) | 96724 (44.6) | 22.3 (102.8) |

$AUC_\infty$, area under the concentration time curve extrapolated to infinity; $C_{max}$, maximum observed concentration; FDC, fixed-dose combination; h, hour; $T_{max}$, time of maximum observed concentration; $T_{1/2}$, terminal elimination half-life.
$C_{max}$, $AUC_\infty$, and $T_{1/2}$ are represented as arithmetic mean (arithmetic CV%). $T_{max}$ is represented as median [minimum–maximum].

### Figure 3. Mean ± SD PK profiles of ROSU following simultaneous or staggered dosing of BEM/RZR FDC




Insert shows mean PK profile (without SD) with truncated X/Y axis to better visualize the transient effect of BEM/RZR on the PK of ROSU.

### Safety and tolerability

- All treatment-emergent adverse events (TEAEs) were mild and resolved by the end of each study
- In Part 1 (DIG), TEAEs were reported in 9/20 (45%) participants overall, with 4/18 (22%) participants reporting TEAEs after DIG only, 3/19 (16%) reporting TEAEs after DIG + BEM/RZR FDC (administered simultaneously) and 5/19 (26%) participants reporting TEAEs after DIG + BEM/RZR FDC (administered staggered)
  - Only headache (5 participants) and dysmenorrhea (2 participants) were reported by at least 2 participants, with no safety patterns identified between dosing sequences
  - One participant discontinued the study due to TEAEs of increased ALT and AST after DIG + BEM/RZR FDC (administered staggered), which resolved 11 days after onset
- In Part 2 (ROSU), TEAEs were reported in 4/18 (22%) participants overall, with no participants reporting TEAEs after ROSU only, 3/18 (17%) reporting TEAEs after ROSU + BEM/RZR FDC (administered simultaneously) and 1/17 (6%) participants reporting TEAEs after ROSU + BEM/RZR FDC (administered staggered)
  - Only headache (2 participants) and nausea (2 participants) were reported by at least 2 participants, with no safety patterns identified between dosing sequences
- There were no clinically significant effects on vital signs, ECG, or laboratory parameters in either study

## CONCLUSIONS

- Overall, a single dose of BEM 550 mg/RZR 180 mg administered as 2 × FDC tablets with DIG or ROSU was well tolerated among healthy participants, with all TEAEs mild in severity
- A single dose of BEM/RZR FDC only slightly increased the plasma exposure of the P-gp and BCRP/OATP1B1/3 index drugs DIG and ROSU
- BEM/RZR FDC has a low potential to exhibit clinically meaningful inhibition of these drug transporters, with a GMR <2
- Dose adjustments are unlikely to be needed for drugs that are sensitive substrates of P-gp or BCRP/OAT1B1/3 when coadministered with BEM/RZR FDC; staggered dosing may lessen any DDI risk

## References

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## Disclosures

XJZ, MM, KP, BB, SL, DJ, MAH, and JH are employees of and may own stock in Atea Pharmaceuticals. GM, principal investigator of the study, is an employee of Altasciences, which was contracted to perform this Phase 1 study.

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