#513 Bemnifosbuvir Has Low Potential to Interfere With P-gp, BCRP, and OATP1B1-mediated Transport

Results From Phase 1 Studies in Healthy Participants

Xiao-Jian Zhou,[1] Gaetano Morelli,[2] Maureen Montrond,[1] Shannan Lynch,[1] Keith Pietropaolo,[1] Bruce Belanger,[1] Arantxa Horga,[1] Janet Hammond[1]

[1]Atea Pharmaceuticals, Boston, MA, USA; [2]Altasciences Company, Quebec, Canada

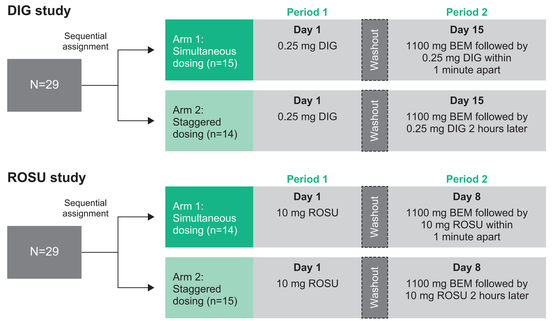
BACKGROUND

- Bemnifosbuvir (BEM) is a guanosine nucleotide prodrug in development for the treatment of COVID-19 and chronic hepatitis C virus (HCV) infection[1,2]
- BEM is rapidly absorbed after oral administration in humans[3] and sequentially metabolized to its active triphosphate inside target cells[1,2]
- BEM was identified *in vitro* as an inhibitor of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and, to a lesser extent, organic anion transporter polypeptide 1B1 (OATP1B1)[4]
  - Efflux transporters P-gp/BCRP have a wide substrate spectrum from different drug classes, including immunosuppressants, antineoplastic drugs, calcium channel blockers, macrolide antibiotics, protease inhibitors, statins, etc.
  - OATP1B1 plays a key role in the hepatic uptake of xenobiotics, including statins, angiotensin II receptor blockers, the meglitinide-class antidiabetics, cytotoxic chemotherapeutic agents, etc.
  - Many of these drugs are commonly prescribed among high-risk COVID-19 patients
- Phase 1, open-label, drug–drug interaction (DDI) studies in healthy participants were conducted to assess the clinical relevance of *in vitro* transporter inhibition by BEM using digoxin (DIG) and rosuvastatin (ROSU) as P-gp and BCRP/OATP1B1 index substrates, respectively[5–7]

METHODS

- Study design: 29 eligible, healthy participants aged 18–65 years were enrolled into each DDI study and assigned to receive DIG or ROSU alone in period 1, followed by simultaneous (Arm 1) or staggered (Arm 2) administration of BEM with DIG or ROSU in period 2, as shown below in **Figure 1**

Figure 1. Treatment schedules for the DIG and ROSU DDI studies



- Plasma samples were collected prior to and over 72 hours post dosing in each period for both DIG and ROSU
- DIG and ROSU were quantitated using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methodologies
- Pharmacokinetic (PK) analyses were performed using non-compartmental approaches
- DDIs were assessed by mixed-model analysis of variance (ANOVA) on the natural log-transformed PK parameters 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

RESULTS

Analysis populations

- 28/29 (97%) participants completed the dosing schedule in each of the studies
- The safety populations included 29 participants who received at least one dose of any study drug (DIG/ROSU and BEM)
- The PK populations included all participants who received at least one dose of DIG/ROSU and had at least one post-dose PK sample collected and analyzed

Demographics

- Participants were generally matched across cohorts in both studies **(Table 1)**
- Mean age was 39.8 years and 49.5 years in the DIG and ROSU studies, respectively
- In both studies, participants were mostly male, White, and non-Hispanic/Latino

Table 1. Demographic characteristics

Characteristic	DIG study [N=29]	ROSU study [N=29]
Mean age, years (SD, min–max)	39.8 (8.75, 23–54)	49.5 (12.6, 24–63)
Sex, n (%)		
Male	17 (58.6)	19 (65.5)
Female	12 (41.4)	10 (34.5)
Race, n (%)		
Asian	2 (6.9)	1 (3.4)
Black or African American	2 (6.9)	4 (13.8)
White	24 (82.8)	24 (82.8)
Other	1 (3.4)	N/A
Mean weight, kg (SD, min–max)	73.3 (14.8, 53.9–104.0)	73.8 (11.8, 51.6–98.4)
Mean BMI, kg/m^2 (SD, min–max)	25.1 (4.1, 18.9–31.9)	25.3 (2.2, 20.9–28.9)

BMI, body mass index; max, maximum; min, minimum; N/A, non-applicable; SD, standard deviation.

Safety/tolerability

- Most treatment-emergent adverse events (TEAEs) were of mild severity and resolved by the end of both studies. There were no serious AEs reported in either study
- Drug-related TEAEs were reported in 12/29 (41.4%) participants over the course of the DIG study **(Table 2)**
  - The most frequently reported TEAEs in participants who received DIG + BEM (simultaneous or staggered) were headache, dizziness, and nausea
  - Proportionately more participants experienced these TEAEs when BEM and DIG were administered simultaneously vs staggered
- In the ROSU study, drug-related TEAEs were reported in 3/29 (10.3%) participants **(Table 3)**
  - The most frequently reported TEAEs in participants who received ROSU + BEM (simultaneous or staggered) were headache and vessel puncture site pain
- No effects on vital signs or ECGs and no drug discontinuations due to an AE were reported
  - In the DIG study, one participant was withdrawn from the study by the sponsor after experiencing emesis approximately 1.5 hours after receiving DIG on Day 1. An additional participant was enrolled in Arm 1 as a replacement

Table 2. Summary of TEAEs (DIG + BEM)

Parameter	DIG alone* [N=29]	Simultaneous DIG + BEM [N=14]	Staggered DIG + BEM [N=14]	Overall [N=29]
Participants with ≥1 drug-related TEAE, n (%)	2 (6.9)	8 (57.1)	2 (14.3)	12 (41.4)
TEAEs reported by ≥2 participants, n (%)				
Headache	3 (10.3)	5 (35.7)	1 (7.1)	9 (31.0)
Dizziness	1 (3.4)	2 (14.3)	1 (7.1)	4 (13.8)
Nausea	1 (3.4)	3 (21.4)	0	4 (13.8)
Thirst	1 (3.4)	2 (14.3)	0	2 (6.9)
Somnolence	1 (3.4)	0	1 (7.1)	2 (6.9)

*Pooled from Arms 1 and 2.

Table 3. Summary of TEAEs (ROSU + BEM)

Parameter	ROSU alone* [N=29]	Simultaneous ROSU + BEM [N=14]	Staggered ROSU + BEM [N=14]	Overall [N=29]
Participants with ≥1 drug-related TEAE, n (%)	0	1 (7.1)	2 (14.3)	3 (10.3)
TEAEs reported by ≥2 participants, n (%)				
Headache	1 (3.4)	2 (14.3)	2 (14.3)	5 (17.2)
Vessel puncture site pain	2 (6.9)	1 (7.1)	0	3 (10.3)
Nausea	0	1 (7.1)	1 (7.1)	2 (6.9)
Diarrhea	2 (6.9)	0	0	2 (6.9)
Skin procedural complication	2 (6.9)	0	0	2 (6.9)

*Pooled from Arms 1 and 2.

DDI evaluation

DIG study

- A single simultaneous high dose of BEM 1100 mg increased the maximum plasma concentration (C_{max}) of DIG by 78%, with minimal effect on its $AUC_{0-\infty}$ **(Tables 4 and 5)**
- When dosing was staggered, BEM did not affect the C_{max} or $AUC_{0-\infty}$ of DIG **(Table 4, Figure 2)**

Table 4. Analysis of DIG study DDI (DIG + BEM on Day 15 vs DIG alone on Day 1)

Treatment	GMR (90% CI)	
	C_{max}	$AUC_{0-\infty}$
Arm 1: Simultaneous dosing	1.78 (1.52–2.09)	1.06 (0.97–1.16)
Arm 2: Staggered dosing	1.03 (0.94–1.13)	0.95 (0.86–1.05)

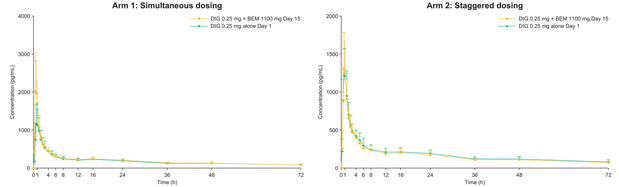
$AUC_{0-\infty}$, area under the concentration time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio.

Table 5. Summary of DIG PK parameters

Treatment		C_{max} (pg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (pg/mL×h)	$t_{1/2}$ (h)
Arm 1: Simultaneous dosing	DIG alone	1242±456	1.0 [0.8–2.0]	18365±4700	42.8±14.7
	DIG + BEM	2236 ±841	0.7 [0.5–1.0]	19662±4148	40.7±11.6
Arm 2: Staggered dosing	DIG alone	1320±381	0.8 [0.8–2.0]	16762±4407	39.1±7.71
	DIG + BEM	1384±470	1.0 [0.5–1.5]	16109±3176	41.2±12.4

C_{max}, $AUC_{0-\infty}$, and $T_{1/2}$ are represented as mean±SD. T_{max} is represented as median [minimum–maximum].
$AUC_{0-\infty}$, area under the concentration time curve extrapolated to infinity; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of maximum observed concentration.

Figure 2. Mean±SD PK profiles of DIG in the absence and presence of BEM



ROSU study

- A single simultaneous high dose of BEM 1100 mg increased the C_{max} of ROSU by 40%, whereas staggered BEM had much less impact **(Tables 6 and 7)**
- Simultaneous or staggered administration of BEM only slightly increased the $AUC_{0-\infty}$ of ROSU (<20%) **(Table 6, Figure 3)**
- As shown in **Figure 2** (DIG) and **Figure 3** (ROSU), the inhibitory effect of BEM on the transporters, while minimal, was transient and more pronounced during absorption
- Staggered dosing was effective in mitigating DDI, if deemed necessary, due to the fast absorption of BEM

Table 6. Analysis of ROSU study DDI (ROSU + BEM Day 8 vs ROSU alone on Day 1)

Treatment	GMR (90% CI)	
	C_{max}	$AUC_{0-\infty}$
Arm 1: Simultaneous dosing	1.40 (1.13–1.75)	1.16 (0.98–1.37)
Arm 2: Staggered dosing	1.20 (1.02–1.40)	1.18 (1.00–1.40)

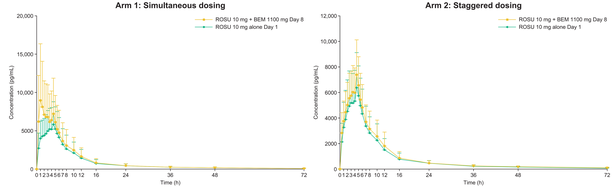
$AUC_{0-\infty}$, area under the concentration time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio.

Table 7. Summary of ROSU PK parameters

Treatment		C_{max} (pg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (pg/mL×h)	$t_{1/2}$ (h)
Arm 1: Simultaneous dosing	ROSU alone	6380±3154	4.5 (0.5–5.0)	67654±33347	40.8±65.1
	ROSU + BEM	9866±7112	2.5 (0.5–5.0)	79994±43906	32.4±26.7
Arm 2: Staggered dosing	ROSU alone	6526±2863	4.5 (2.6–5.0)	64331±25806	26.6±16.9
	ROSU + BEM	7572±2647	4.5 (3.5–5.0)	74744±24211	28.9±15.1

C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ are represented as mean±SD. T_{max} is represented as median (minimum–maximum).
$AUC_{0-\infty}$, area under the concentration time curve extrapolated to infinity; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of maximum observed concentration.

Figure 3. Mean±SD PK profiles of ROSU in the absence and presence of BEM



CONCLUSIONS

- A single high dose of BEM only slightly increased the plasma exposure of the P-gp and BCRP/OATP1B1 index substrates, DIG and ROSU
- BEM has low potential to exhibit clinically meaningful inhibition on these drug transporters
- The safety and tolerability profiles of DIG and ROSU were mostly comparable when administered alone or with BEM (simultaneous or staggered)
- Dose adjustments are unlikely to be required for drugs that are sensitive substrates of P-gp or BCRP/OATP1B1 when co-administered with BEM; however, staggered dosing may reduce any risk of DDI

References

1. Good SS, et al. Antimicrob Agents Chemother 2021;65:e02479–20; 2. Good SS, et al. PLoS One 2020;15:e0227104; 3. Bertiba E, et al. Antimicrob Agents Chemother 2019;63:e01201–19; 4. Data on File. Atea Pharmaceuticals; 5. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. FDA, August 2022. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers (accessed Feb 2023); 6. NCT05137626. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05137626 (accessed Feb 2023); 7. NCT05154123. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05154123 (accessed Feb 2023).

Acknowledgments

This study was funded by Atea Pharmaceuticals. Medical writing and design support were provided by Elements Communications Ltd, Westerham, UK and were funded by Atea Pharmaceuticals.

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 studies, is an employee of Altasciences Company Inc, Quebec, Canada, which was contracted to perform these Phase 1 studies.

Poster presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI) 2023 Conference, 19–22 February, Seattle, USA.