Pharmacokinetics of Bemnifosbuvir in Participants with Hepatic Impairment

Xiao-Jian Zhou,[1] Thomas Marbury,[2] Juan Carlos Rondon,[3] William Smith,[4] Maureen Montrond,[1] Shannan Lynch,[1] Keith Pietropaolo,[1] Bruce Belanger,[1] Maria Arantxa Horga,[1] and Janet Hammond[1]

1. Atea Pharmaceuticals Inc, Boston, USA; 2. Orlando Clinical Research Center, Orlando, USA; 3. Clinical Pharmacology of Miami LLC, Miami, USA; 4. Alliance for Multispecialty Research LLC, Knoxville, USA.

WED-278

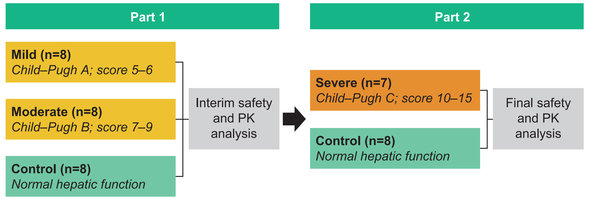
INTRODUCTION

- Bemnifosbuvir (BEM, AT-527) is an oral double prodrug of a guanosine nucleotide analog with potent activity against flaviviruses including hepatitis C virus (HCV)[1]
- Combination of BEM 550 mg and ruzasvir (an inhibitor of HCV NS5A) 180 mg, administered orally once daily as a fixed-dose tablet is being evaluated in Phase 3 clinical trials for the treatment of chronic HCV[2]
- Hepatic impairment may influence the pharmacokinetics (PK) and, potentially, the safety and/or efficacy of direct-acting antiviral drugs.[3] Therefore, we evaluated the effect of hepatic impairment on the PK of BEM in a Phase 1 study (NCT05724693)

METHODS

- The study (N=39) enrolled 23 HCV-negative participants with either mild (n=8), moderate (n=8), or severe (n=7) hepatic impairment, as well as 16 control participants (HCV-negative and normal hepatic function) matched by gender, age (±10 years), and body mass index (BMI; ±20%) (**Figure 1**)
- Participants received a single oral dose of BEM 550 mg under fasted conditions and intensive PK sampling was performed over 120 hours, with plasma concentrations of BEM and its metabolites (AT-551, AT-229 and AT-273) quantitated using validated bioanalytical methods. Plasma protein binding of BEM was assessed 0.5 hours after dosing
- Safety assessments included vital signs, physical examinations, 12-lead ECGs, clinical laboratory tests and adverse event (AE) monitoring throughout the study

Figure 1. Study design



The adaptive study design allowed for an interim analysis after completion of Part 1, prior to enrollment of Part 2.

RESULTS

Participant disposition and baseline characteristics

- Of the 39 participants enrolled, 37 completed the study per protocol: one participant prematurely withdrew due to an AE (COVID-19 infection after BEM administration), and one participant was lost to follow-up
- All 39 participants received the study drug and had ≥1 post-dose PK sample evaluated, and so were included in the PK and safety analysis populations
- Baseline demographics were generally balanced across the hepatic impairment and control groups (**Table 1**)

Table 1. Baseline demographic and clinical characteristics

Characteristics	Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=7)
Median age, years (range)	61.0 (56–68)	62.0 (42–69)	65.0 (51–71)	60.0 (55–70)
Male sex, n (%)	8 (50)	3 (37.5)	2 (25.0)	5 (71.4)
Race, n (%)				
Asian	0	1 (12.5)	0	0
Black or African American	2 (12.5)	2 (25.0)	0	1 (14.3)
White	14 (87.5)	5 (62.5)	8 (100.0)	6 (85.7)
Ethnicity, n (%)				
Hispanic/Latino	7 (43.8)	3 (37.5)	5 (62.5)	3 (42.9)
Not Hispanic/Latino	9 (56.3)	5 (62.5)	3 (37.5)	4 (57.1)
Mean BMI, kg/m² (SD)	28.4 (3.5)	29.1 (6.3)	29.8 (6.0)	26.6 (2.9)
Median Child–Pugh score (range)	N/A	6.0 (5–6)	7.0 (7–9)	11.0 (10–13)

BMI, Body mass index; N/A, not applicable; SD, standard deviation.

Safety and tolerability

- A total of four treatment-emergent AEs (TEAEs) were reported for three of the 39 participants in the study (7.7%)
- One participant with mild hepatic impairment experienced headache and dysuria. In the normal hepatic function group, one participant experienced headache and one was withdrawn due to COVID-19
- All four TEAEs were Grade 1/2, with the two headaches deemed related to BEM; no deaths or serious AEs occurred in the study
- There were no clinically significant changes in laboratory values, vital signs, or ECG changes from baseline reported during the study

PK evaluation

- Plasma concentration–time profiles for BEM and its metabolites are presented in **Figure 2**. Summary PK results and comparative statistics are presented in **Table 2** and **Table 3**, respectively
- There was no significant effect of hepatic impairment on the time to peak exposure (T_{max}) of BEM or its metabolites
- Mild hepatic impairment had minimal effect on the PK of BEM. However, peak and total plasma exposure to BEM increased as hepatic function deteriorated, by up to ~80% and ~160%, respectively, in participants with severe impairment
  - There was a shallow relationship between exposure to BEM and Child–Pugh scores, which was significant for AUC_{∞} (slope=0.109; P=0.01)

Table 2. Summary of key PK results for BEM and its metabolites

Parameter	Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=7)
BEM				
T_{max} (h)	0.5 (0.3–1.0)	0.5 (0.3–0.8)	0.5 (0.3–0.6)	0.5 (0.3–0.5)
C_{max} (ng/mL)	4342 (38.6)	5146 (24.0)	6246 (51.3)	7257 (32.1)
AUC_{∞} (ng/mL×h)	2923 (37.2)	3619 (33.1)	4271 (49.4)	7167 (43.4)
$T_{1/2}$ (h)	1.21 (27.4)	1.15 (38.0)	1.12 (25.4)	1.00 (24.0)
AT-551				
T_{max} (h)	0.8 (0.5–2.0)	1.0 (0.5–1.0)	1.0 (0.8–2.0)	1.0 (0.8–2.0)
C_{max} (ng/mL)	780 (44.7)	1022 (48.5)	977 (33.9)	699 (38.3)
AUC_{∞} (ng/mL×h)	2267 (40.0)	2879 (37.9)	3259 (31.0)	3557 (36.6)
$T_{1/2}$ (h)	2.83 (16.4)	2.82 (24.7)	2.80 (24.9)	2.98 (41.3)
AT-229				
T_{max} (h)	2.0 (1.0–4.0)	1.0 (1.0–5.0)	2.0 (1.0–2.0)	2.0 (1.0–4.0)
C_{max} (ng/mL)	1028 (30.3)	1089 (37.0)	1017 (41.1)	943 (57.9)
AUC_{∞} (ng/mL×h)	8342 (29.5)	7006 (52.8)	7483 (36.2)	9665 (79.7)
$T_{1/2}$ (h)	12.50 (55.7)	7.47 (59.6)	11.10 (58.8)	9.10 (38.1)
AT-273				
T_{max} (h)	4.5 (3.0–8.0)	4.0 (3.0–5.0)	5.0 (4.0–6.0)	6.0 (4.0–10)
C_{max} (ng/mL)	205 (23.1)	255 (28.7)	248 (34.0)	232 (35.9)
AUC_{∞} (ng/mL×h)	3824 (32.4)	3406 (29.7)	4005 (38.3)	5116 (81.3)
$T_{1/2}$ (h)	15.60 (47.7)	13.30 (39.3)	20.40 (48.1)	18.80 (60.1)

Parameters are shown as mean (%CV), except for T_{max} where median (range) are presented.

Figure 2. Plasma concentration–time profiles for BEM and its metabolites

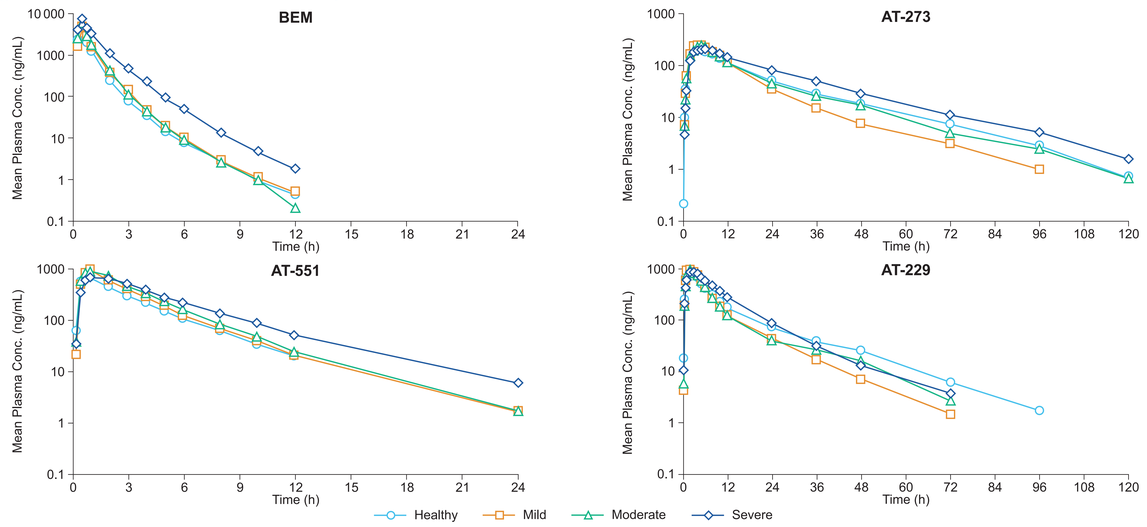


Table 3. Comparative PK statistics (impaired vs normal) for BEM and its metabolites

Analytes	Hepatic impairment category	GMR (90% CI) C_{max}	GMR (90% CI) AUC_{∞}
BEM	**Mild**	1.31 (0.92–1.86)	1.34 (0.92–1.94)
	Moderate	1.46 (1.03–2.07)	1.49 (1.03–2.17)
	Severe	1.81 (1.25–2.61)	2.58 (1.75–3.82)
AT-551	**Mild**	1.36 (0.97–1.89)	1.28 (0.97–1.69)
	Moderate	1.34 (0.96–1.86)	1.48 (1.12–1.95)
	Severe	0.95 (0.67–1.34)	1.58 (1.19–2.11)
AT-229	**Mild**	1.03 (0.77–1.39)	0.77 (0.55–1.09)
	Moderate	0.97 (0.72–1.30)	0.89 (0.62–1.26)
	Severe	0.85 (0.62–1.15)	0.98 (0.69–1.40)
AT-273	**Mild**	1.23 (0.99–1.53)	0.89 (0.66–1.19)
	Moderate	1.18 (0.95–1.46)	1.02 (0.75–1.39)
	Severe	1.10 (0.88–1.38)	1.15 (0.84–1.57)

GMR, geometric mean ratio (comparison vs normal hepatic function).

- Hepatic impairment had minimal effect on the peak exposure of the L-alanyl intermediate AT-551 whereas total exposure to AT-551 increased by ~50% and ~60% with moderate and severe impairment, respectively
- There was no significant effect of hepatic impairment on peak or total exposure to AT-229 (a nucleoside metabolite) and AT-273 (the plasma surrogate for the intracellular active triphosphate)
- The mean fraction of BEM unbound to human plasma protein was similar among the studied groups: 18.5, 19.7, 21.2 and 27.4%, respectively, in participants with normal hepatic function, or mild, moderate and severe hepatic impairment
- Hepatic impairment had no apparent effect on the half-lives of BEM and its metabolites

CONCLUSIONS

- BEM was safe and well tolerated
  - There were no differences in safety/tolerability outcomes between participants with hepatic impairment and normal hepatic function
- Hepatic impairment resulted in increased peak and total exposure to BEM, compared with normal hepatic function, following a single oral dose of BEM 550 mg under fasted conditions
  - The magnitude of this effect was greater in participants with severe hepatic impairment vs mild/moderate impairment
- Hepatic impairment did not significantly impact the exposure to AT-273, the surrogate of the active triphosphate, indicating that hepatic impairment does not impact the antiviral activity of BEM
- These data indicate that no dose adjustment for BEM is needed in participants with hepatic impairment

References

1. Berliba E, et al. Antimicrob Agents Chemother 2019;63:e01201–19
2. Good SS, et al. Antiviral Res 2025;237:106137
3. Smolders EJ, et al. Drug Saf 2016;39:589–611

Acknowledgments

This study was funded by Atea Pharmaceuticals (Boston, USA). Medical writing and design support were provided by Obsidian Healthcare Group (London, UK) and were funded by Atea Pharmaceuticals.

Disclosures

XJZ, MM, SL, KP, BB, MAH and JH are employees of and may own stock in Atea Pharmaceuticals.

Poster presented at The European Association for the Study of the Liver (EASL) Congress, May 7–10 2025, Amsterdam, The Netherlands.