Pharmacokinetics of Bemnifosbuvir in Participants With Renal Impairment

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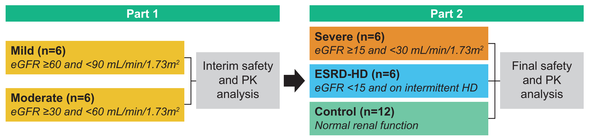
INTRODUCTION

- 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 under Phase 3 clinical development for the treatment of chronic HCV[2]
- Renal impairment of various degrees, including end-stage renal disease (ESRD) requiring hemodialysis (HD), may influence the pharmacokinetics (PK) and, potentially, the safety and/or efficacy of direct-acting antiviral drugs.[3] Therefore, we evaluated the effect of renal impairment on the PK of BEM in a Phase 1 study (NCT05618314)

METHODS

- The study (N=36) enrolled 24 HCV-negative participants with either mild (n=6), moderate (n=6), or severe renal impairment (n=6), or ESRD undergoing HD (n=6), as well as 12 healthy control participants (HCV-negative and normal renal function) matched by gender, age (±10 years), and body mass index (BMI; ±20%) (**Figure 1**)
- Participants not undergoing HD received a single oral dose of BEM 550 mg under fasted conditions. Participants with ESRD received a single dose of BEM 550 mg ~2 hours prior to HD (pre-dialysis) and a second dose of BEM 15 days later, ~2 hours after completing HD (post-dialysis)
  - The metabolite AT-273 is a substrate of OAT1 and OAT3 (organic anion transporters) *in vitro*. To assess the clinical relevance of these findings, the control subjects also received a second dose of BEM on Day 15 with concomitant probenecid (500 mg BID), an inhibitor of OAT1 and OAT3
- 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.
eGFR, estimated glomerular filtration rate.

RESULTS

Subject disposition and baseline characteristics

- Of the 36 participants enrolled, 34 completed the study per protocol. All 36 patients received the study drug and had ≥1 post-dose PK sample evaluated, and were all included in the PK and safety analysis populations
- Baseline demographics were generally balanced across the renal impairment and control groups (**Table 1**)

Table 1. Baseline demographic and clinical characteristics

Characteristic	Normal (n=12)	Mild (n=6)	Moderate (n=6)	Severe (n=6)	ESRD-HD (n=6)
Median eGFR, mL/min (range)	104 (94.8–141)	84.6 (57.7–96.4)	53.7 (41.4–60.1)	23.7 (19.1–30)	NA
Median age, years (range)	55.0 (51–71)	60.0 (37–70)	70.5 (61–77)	60.5 (50–66)	55.5 (48–67)
Male sex, n (%)	6 (50.0)	4 (66.7)	2 (33.3)	3 (50.0)	5 (83.3)
Race, n (%)					
Asian	0	0	0	0	0
Black or African American	1 (8.3)	0	1 (16.7)	1 (16.7)	1 (16.7)
White	11 (91.7)	6 (100.0)	5 (83.3)	5 (83.3)	5 (83.3)
Ethnicity, n (%)					
Hispanic/Latino	2 (16.7)	1 (16.7)	1 (16.7)	0	3 (50.0)
Not Hispanic/Latino	10 (63.3)	5 (83.3)	5 (83.3)	6 (100.0)	3 (50.0)
Mean BMI, kg/m² (SD)	26.1 (2.5)	27.2 (6.3)	27.4 (6.6)	29.3 (4.7)	31.5 (3.6)

eGFR, estimated glomerular filtration rate; NA, not applicable; SD, standard deviation.

Safety and tolerability

- A total of 31 treatment-emergent AEs (TEAEs) were reported for 15 of the 36 participants in the study (41.7%)
- All TEAEs were Grade 1–2 (96.7% Grade 1), and three were deemed possibly related to BEM; no deaths or SAEs occurred in the study
- Two participants (one in the ESRD-HD group and one in the group with normal renal function) experienced Grade 1 nausea; one participant in the group with normal renal function experienced Grade 1 myalgia
- 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
- Compared with the healthy control group, plasma exposure to BEM was not affected by any degree of renal impairment
- Plasma exposure to AT-551 (the L-alanyl intermediate metabolite) was not affected by mild or moderate renal impairment, whereas its overall exposure (AUC_∞) increased by ~2- and ~3-fold in the severe and ESRD-HD (post-dialysis dosing) groups, respectively
- Plasma exposure to AT-229 (an inactive circulating nucleoside metabolite) was not affected by mild renal impairment, but increased as renal function further deteriorated by up to approximately 5.5-fold in the ESRD-HD group with post-dialysis dosing
- Plasma exposure to AT-273 (the inactive plasma circulating guanosine nucleoside metabolite considered a surrogate of the active intracellular triphosphate of the drug), while similar between mild renal impairment and control, increased by ~5.3- and 33-fold in subjects with severe renal impairment and those with ESRD-HD with post-dialysis dosing, respectively
- The plasma half-lives of BEM and its metabolites remained mostly consistent across non-HD participants regardless of renal impairment
- In participants with ESRD-HD, a 4-hour HD removed (based on AUC_∞) approximately 55% of AT-551, and 40% of AT-229 and AT-273, without affecting the parent BEM
- BEM was not highly bound to human plasma protein (about 80%) and the fraction unbound, ranging from ~15 to 20%, was not meaningfully affected by renal impairment

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

Parameter	Normal (N=12)		Mild (N=6)	Moderate (N=6)	Severe (N=6)	ESRD-HD (N=6)	
	Alone	Probenecid				Pre-Dialysis	Post-Dialysis
BEM							
T_{max} (h)	0.5 (0.3–0.8)	0.5 (0.3–0.5)	0.4 (0.3–0.5)	0.5 (0.5–0.8)	0.3 (0.3–0.8)	0.6 (0.3–0.8)	0.5 (0.5–0.8)
C_{max} (ng/mL)	5326 (51.2)	5950 (22.1)	4904 (17.5)	6032 (37.2)	5093 (27.4)	4219 (29.9)	5663 (67.6)
AUC_∞ (ng/mL×h)	3754 (46.6)	4325 (24.3)	3700 (24.1)	4344 (43.9)	3973 (15.8)	3638 (38.2)	3759 (51.6)
$T_{1/2}$ (h)	0.86 (23.3)	0.92 (23.9)	0.93 (21.5)	0.94 (23.4)	0.88 (17.0)	1.49 (47.7)	0.95 (21.1)
AT-551							
T_{max} (h)	0.8 (0.8–2.0)	1.0 (0.5–1.5)	0.8 (0.5–1.0)	0.9 (0.8–1.5)	1.0 (0.6–1.1)	1.2 (0.8–2.0)	1.0 (0.5–3.0)
C_{max} (ng/mL)	936 (67.1)	1158 (40.0)	853 (55.1)	790 (27.4)	1102 (31.6)	838 (42.7)	2119 (116)
AUC_∞ (ng/mL×h)	2534 (45.9)	3492 (28.6)	2426 (35.9)	2912 (24.9)	5553 (51.7)	3610 (40.5)	7902 (46.7)
$T_{1/2}$ (h)	2.89 (26.3)	2.91 (13.7)	2.56 (24.6)	3.01 (29.9)	4.35 (19.8)	10.7 (41.6)	10.1 (39.4)
AT-229							
T_{max} (h)	1.5 (1.0–3.0)	1.5 (1.0–3.0)	1.0 (1.0–2.0)	2.5 (1.5–3.0)	3.0 (2.0–4.0)	2.0 (1.4–3.0)	2.2 (0.5–4.0)
C_{max} (ng/mL)	1064 (29.7)	1287 (31.7)	1008 (43.5)	1501 (44.2)	2153 (27.4)	1612 (49.9)	2062 (47.8)
AUC_∞ (ng/mL×h)	6837 (15.0)	11,384 (25.6)	7600 (31.8)	12,100 (33.5)	22,745 (14.5)	24,092 (42.1)	40,110 (42.9)
$T_{1/2}$ (h)	19.1 (68.4)	19.3 (57.6)	19.6 (75.1)	17.0 (67.5)	11.0 (64.7)	8.98 (30.3)	10.3 (28.8)
AT-273							
T_{max} (h)	4.0 (2.1–6.0)	6.0 (4.2–8.0)	4.0 (3.0–6.0)	6.0 (4.0–10)	9.0 (8.0–10)	48 (28–49)	45 (24–48)
C_{max} (ng/mL)	197 (29.5)	298 (29.5)	232 (26.5)	389 (30.9)	559 (15.7)	883 (15.3)	1387 (28.3)
AUC_∞ (ng/mL×h)	3257 (21.9)	6233 (22.9)	4053 (31.8)	7343 (51.8)	17,708 (29.9)	65,771 (13.2)	110,907 (32.4)
$T_{1/2}$ (h)	23.5 (46.0)	30.0 (70.0)	27.7 (74.9)	28.5 (111)	15.7 (19.4)	33.5 (NA)	26.9 (NA)

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

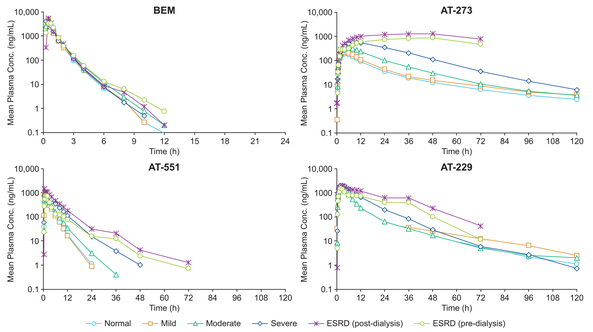


Table 3. Comparative PK statistics (impaired vs normal) for BEM and its metabolites

Analytes	Renal impairment category	GMR (90% CI)	
		C_{max}	AUC_∞
BEM	**Mild**	1.02 (0.57–1.83)	1.06 (0.64–1.73)
	Moderate	1.20 (0.67–2.16)	1.19 (0.72–1.95)
	Severe	1.04 (0.58–1.87)	1.15 (0.70–1.89)
	ESRD (pre-dialysis)	0.86 (0.48–1.55)	1.01 (0.62–1.66)
	ESRD (post-dialysis)	1.01 (0.56–1.81)	1.02 (0.62–1.67)
AT-551	**Mild**	0.94 (0.46–1.93)	0.98 (0.57–1.68)
	Moderate	0.95 (0.46–1.94)	1.21 (0.70–2.07)
	Severe	1.31 (0.64–2.69)	2.12 (1.23–3.64)
	ESRD (pre-dialysis)	0.96 (0.47–1.98)	1.43 (0.83–2.46)
	ESRD (post-dialysis)	1.73 (0.84–3.56)	3.10 (1.81–5.33)
AT-229	**Mild**	0.91 (0.51–1.61)	1.07 (0.72–1.61)
	Moderate	1.37 (0.77–2.42)	1.72 (1.14–2.58)
	Severe	2.06 (1.16–3.65)	3.34 (2.22–5.01)
	ESRD (pre-dialysis)	1.40 (0.79–2.48)	3.35 (2.23–5.03)
	ESRD (post-dialysis)	1.82 (1.02–3.22)	5.48 (3.65–8.22)
AT-273	**Mild**	1.20 (0.81–1.76)	1.22 (0.78–1.91)
	Moderate	1.96 (1.33–2.89)	2.01 (1.28–3.16)
	Severe	2.94 (1.99–4.33)	5.34 (3.41–8.38)
	ESRD (pre-dialysis)	4.64 (3.15–6.84)	20.5 (13.1–32.1)
	ESRD (post-dialysis)	7.08 (4.81–10.4)	33.3 (21.3–52.3)

CI, confidence interval; GMR, geometric mean ratio (comparison vs normal renal function).

- Probenecid, an inhibitor of OAT1/3, while not affecting the plasma PK of BEM, increased the plasma exposure of its metabolites, most notably AT-273 (**Table 4**)

Table 4. Comparative PK statistics (with vs without probenecid)

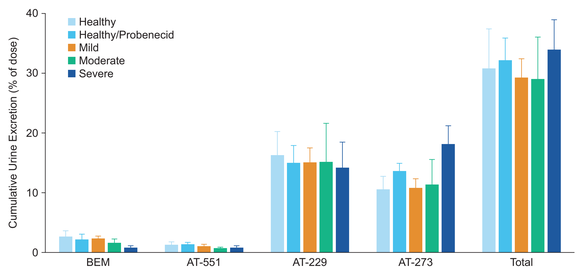
Analytes	GMR (90% CI)	
	C_{max}	AUC_∞
BEM	1.23 (0.91–1.67)	1.23 (0.94–1.62)
AT-551	1.34 (0.95–1.89)	1.44 (1.12–1.85)
AT-229	1.21 (0.95–1.53)	1.64 (1.40–1.91)
AT-273	1.53 (1.22–1.92)	1.90 (1.59–2.27)

GMR, geometric mean ratio (comparison vs no probenecid in participants with normal renal function).

Renal elimination

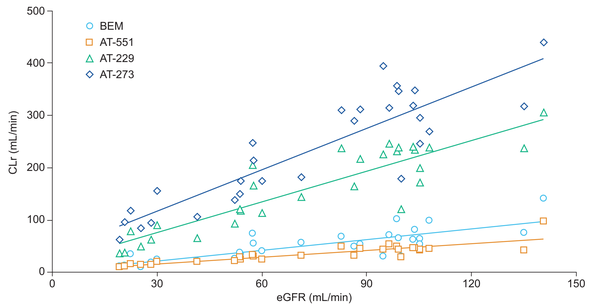
- Cumulative urine excretion for BEM and AT-551 was low, up to ~2.5% and ~1.5%, respectively, of the administered dose (**Figure 3**). Renal excretion of the nucleoside metabolites AT-229 and AT-273 was higher, each representing ~10–15% of the administered dose. Cumulative urine excretion for all analytes was about 30% of dose
- Cumulative urine excretion of BEM and metabolites was mostly unaffected by renal dysfunction
- Renal clearance (CLr) of BEM and AT-551 was low and minimally dependent on eGFR (**Figure 4**). The nucleoside metabolites AT-229 and AT-273 exhibited high CLr, largely driven by eGFR
- AT-229 and AT-273 exhibited CLr exceeding normal eGFR, even in subjects with moderate (AT-229) to severe (AT-273) renal impairment, indicating the involvement of active components in their renal elimination

Figure 3. Cumulative urine excretion of BEM and its metabolites



Data are mean + SD.

Figure 4. Relationship between CLr and eGFR



CONCLUSIONS

- A single dose of BEM 550 mg was safe and well tolerated in participants with normal or impaired renal function, including when co-administered with probenecid (an inhibitor of OAT1/3)
- Renal impairment did not affect the plasma PK of BEM but gradually increased plasma exposure of its inactive nucleoside metabolites as renal impairment worsened
- HD was effective in removing circulating metabolites from participants with ESRD
- The cumulative amount excreted in urine was low for BEM and AT-551, and high for the nucleoside metabolites AT-229 and AT-273
  - AT-229 and AT-273 exhibited renal clearance exceeding eGFR, indicative of active renal secretion
- Probenecid increased the plasma exposure of BEM metabolites, which was deemed not clinically meaningful
- This study provides safety and PK support for dosing BEM in patients with various degrees of renal impairment

References

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Disclosures

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

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