#512 No Dose Adjustments for CYP3A4 Substrates When Co-administered With Bemnifosbuvir

Results From a Phase 1 Study in Healthy Participants

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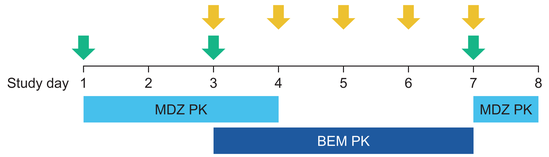
BACKGROUND

- 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 inducer and inhibitor of CYP3A4 (reversible and time-dependent inhibition [TDI])[4]
  - CYP3A4 is involved in the metabolism of many medications from virtually all therapeutic areas, including those that are commonly prescribed among high-risk COVID-19 patients (immunosuppressants, chemotherapeutics, antibiotics, antivirals, statins, antihypertensives, antiarrhythmics, antidepressants, etc.)
- Here we report a Phase 1, open-label, drug–drug interaction (DDI) study in healthy participants using midazolam (MDZ), a sensitive CYP3A4 substrate, as an index drug[5,6]

METHODS

- 24 eligible, healthy adult participants were enrolled and assigned to one of two arms (n=12 per arm). Both groups received a single dose of 2 mg MDZ alone on Day 1 **(Figure 1)**
- On Days 3–7 inclusive, all participants received oral BEM 550 mg twice daily (BID)
- On Day 3 and Day 7:
  - Arm 1 received a single dose of 2 mg MDZ simultaneously with BEM (simultaneous administration)
  - Arm 2 received BEM and then a single dose of 2 mg MDZ 2 hours later (staggered administration)

Figure 1. Study schema: Arm 1 and Arm 2 (N=24, 12 per arm)



*On Day 3 and Day 7, Arm 1 was administered BEM simultaneously with MDZ in the morning (within 1 minute apart); Arm 2 was administered BEM in the morning, 2 hours (± 5 minutes) prior to MDZ administration.
AM, morning; PK, pharmacokinetics; PM, evening; SD, single dose.

- Plasma sample collection
  - MDZ and 1-hydroxymidazolam (1-OH-MDZ) in Arm 1 and Arm 2: serial plasma samples were collected prior to and over 24 hours post MDZ dosing on Day 1 (MDZ alone), Day 3 (MDZ with a single dose of BEM), and Day 7 (MDZ with repeat dose of BEM)
  - BEM and metabolites in Arm 1: serial plasma samples were collected prior to and over the 12-hour BEM dosing interval on the mornings of Day 6 (BEM alone) and Day 7 (BEM with MDZ)
- MDZ/1-OH-MDZ and BEM/metabolites (AT-511, AT-551, AT-229, and AT-273) 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 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, oxygen saturation, physical examination, neurologic examination, electrocardiograms (ECGs), and standard clinical laboratory tests

RESULTS

Demographics

- Participants were mostly male (79.2%) and White (87.5%) with a mean age of 41.2 years and mean body mass index (BMI) of 24.6 kg/m^2 **(Table 1)**

Table 1. Demographic characteristics

Characteristic	Total population [N=24]
Mean age, years (SD, min–max)	41.2 (14.0, 20–64)
Sex, n (%)	
Male	19 (79.2)
Female	5 (20.8)
Race, n (%)	
White	21 (87.5)
Black or African American	3 (12.5)
Mean weight, kg (SD, min–max)	74.1 (11.9, 52.1–92.6)
Mean BMI, kg/m^2 (SD, min–max)	24.6 (2.7, 20.3–29.7)

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

Safety/tolerability

- BEM was well tolerated in healthy adults when administered alone or with MDZ (simultaneous or staggered administration)
- Most treatment-emergent adverse events (TEAEs) were of mild severity (93.8%) and unrelated to treatments (62.5%). No serious AEs were reported
- The most commonly reported TEAEs were somnolence in 5/24 (20.8%) participants and headache in 3/24 (12.5%) participants **(Table 2)**
- Drug-related TEAEs were reported in 9/24 (37.5%) participants over the course of the study, of which 8/9 (88.9%) TEAEs were related to MDZ **(Table 2)**
- There were no clinically significant abnormal effects on vital signs or ECGs; one participant did not receive the last dose of BEM on Day 7 due to an AE of abdominal pain (resolved by end of study), which led to study discontinuation

Table 2. Summary of TEAEs

Parameter	Days 1–3	Days 3–8		Overall [N=24]
	MDZ alone* [N=24]	Simultaneous MDZ + BEM [N=12]	Staggered MDZ + BEM [N=12]	
Participants with ≥1 drug-related TEAE, n (%)				
Related to MDZ	0	7 (58.3)	1 (8.3)	8 (33.3)
Related to BEM	0	1 (8.3)	0	1 (4.2)
TEAEs reported by ≥2 participants, n (%)				
Somnolence	0	5 (41.7)	0	5 (20.8)
Headache	1 (4.2)	2 (16.7)	0	3 (12.5)
Dizziness	1 (4.2)	0	1 (8.3)	2 (8.3)
Rash	0	1 (8.3)	1 (8.3)	2 (8.3)
Abdominal pain	0	2 (16.7)	0	2 (8.3)

Percentages are based on the number of participants in the safety population in each arm.
*Pooled from Arms 1 and 2.

DDI evaluation

- A single simultaneous or staggered dose of BEM increased the plasma exposure of MDZ by 14–26% **(Table 3)**
- Staggered administration of a single dose of BEM had less impact on 1-OH-MDZ than simultaneous dosing, increasing plasma exposure by 8–17% vs 22–31%, respectively **(Table 3, Figure 2)**
- Inhibitory effect of BEM was more pronounced with repeat dosing, consistent with *in vitro* data showing TDI of CYP3A4 **(Table 3, Figure 2)**
- After repeat dosing, simultaneously administered BEM increased plasma MDZ exposure by 83–98%, without substantially affecting the exposure of 1-OH-MDZ (increased by 20–27%) **(Table 3)**
- With repeat dosing, staggered BEM showed less effect on both MDZ and 1-OH-MDZ vs simultaneous administration **(Figure 2)**
- A single dose of MDZ had no effect on the steady-state PK of BEM **(Table 5, Figure 3)**

Table 3. Summary of statistical analysis of the effect of BEM on the plasma PK of MDZ/1-OH-MDZ

Comparison	Analyte	GMR [90% CI]	
		C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL×h)
Arm 1: Simultaneous dosing			
Competitive inhibition:			
MDZ + BEM single dose (Day 3) vs MDZ alone (Day 1)	1-OH-MDZ	1.31 [1.05–1.63]	1.22 [0.93–1.60]
TDI/induction:			
MDZ + BEM repeat dose (Day 7) vs MDZ alone (Day 1)	1-OH-MDZ	1.20 [0.96–1.51]	1.27 [1.07–1.51]
TDI/induction/competitive inhibition:			
MDZ + BEM repeat dose (Day 7) vs MDZ + BEM single dose (Day 3)	1-OH-MDZ	0.91 [0.72–1.15]	1.09 [0.93–1.26]
Arm 2: Staggered dosing			
Competitive inhibition:			
MDZ + BEM single dose (Day 3) vs MDZ alone (Day 1)	1-OH-MDZ	1.17 [1.00–1.37]	1.08 [0.98–1.20]
TDI/induction:			
MDZ + BEM repeat dose (Day 7) vs MDZ alone (Day 1)	1-OH-MDZ	0.99 [0.85–1.14]	1.34 [1.02–1.76]
TDI/induction/competitive inhibition:			
MDZ + BEM repeat dose (Day 7) vs MDZ + BEM single dose (Day 3)	1-OH-MDZ	0.84 [0.73–0.97]	1.09 [0.88–1.36]

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

Table 4. Summary PK parameters of MDZ and 1-OH-MDZ in the absence and presence of BEM

Treatment	Analyte	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL×h)	$t_{1/2}$ (h)
Arm 1: Simultaneous dosing					
MDZ alone (Day 1)	MDZ	0.5 [0.3–1.0]	10.7±3.8	30.1±7.1 (7)	4.8±2.3 (7)
	1-OH-MDZ	0.5 [0.5–1.5]	4.0±1.9	10.6±3.3 (4)	3.5±1.8 (4)
MDZ + BEM (Day 3)	MDZ	0.5 [0.3–1.0]	13.2±4.3	37.9±8.1 (7)	5.0±1.7 (7)
	1-OH-MDZ	0.5 [0.5–1.5]	5.1±2.0	13.0±2.3 (5)	4.3±2.4 (5)
MDZ + BEM (Day 7)	MDZ	0.5 [0.5–1.0] (11)	19.5±6.6 (11)	59.1±12.0 (8)	5.8±0.9 (8)
	1-OH-MDZ	0.5 [0.5–1.0] (11)	4.6±1.7 (11)	13.4±2.5 (7)	4.9±1.7 (7)
Arm 2: Staggered dosing					
MDZ alone (Day 1)	MDZ	0.8 [0.5–1.0]	9.7±3.0	25.2±11.5 (5)	3.9±1.9 (5)
	1-OH-MDZ	1.0 [0.5–1.0]	4.2±1.7	8.8±4.3 (7)	3.1±1.3 (7)
MDZ + BEM (Day 3)	MDZ	1.0 [0.5–1.1]	12.3±4.1	29.6±15.8 (6)	2.8±1.5 (6)
	1-OH-MDZ	1.0 [0.5–1.1]	4.7±1.5	10.4±3.7 (8)	3.2±1.6 (8)
MDZ + BEM (Day 7)	MDZ	0.5 [0.5–1.5]	14.8±8.7	33.7±13.3 (9)	4.2±1.7 (9)
	1-OH-MDZ	1.0 [0.5–1.5]	4.0±1.4	10.8±3.6 (8)	3.5±1.9 (8)

Data are presented as mean±SD. T_{max} is presented as median [minimum–maximum]. n=12 unless specified in parentheses.
$AUC_{0-\infty}$, area under the curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life.

Table 5. Summary steady-state PK parameters of BEM and metabolites following administration of BEM alone on Day 6 and with simultaneous MDZ on Day 7 (Arm 1)

Treatment	Analyte	T_{max} (h)	C_{max} (ng/mL)	AUC_{τ} (ng/mL×h)
BEM alone (Day 6)*	AT-511	0.5 [0.3–1.0]	5493±2957	3959±2140
	AT-551	1.0 [0.5–1.5]	740.0±246.0	2141±666.8
	AT-229	1.5 [1.0–2.0]	1303±376.3	8380±1753
	AT-273	4.0 [3.0–4.0]	312.5±95.7	2918±978.1
BEM + MDZ (Day 7)†	AT-511	0.5 [0.3–1.5]	5469±2501	4706±1765
	AT-551	1.1 [0.6–2.0]	616.2±153.1	2048±464.5
	AT-229	2.0 [1.0–3.0]	1339±311.8	9625±1468
	AT-273	4.0 [2.0–4.1]	349.7±87.3	3368±881.9

Data are presented as mean±SD. T_{max} is presented as median [minimum–maximum].
*n=12; †n=11.
AUC_{τ}, area under the curve over the dosing interval; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to reach maximum concentration.

Figure 2. Mean±SD plasma concentration vs time profiles of MDZ/1-OH-MDZ in the absence and presence of BEM

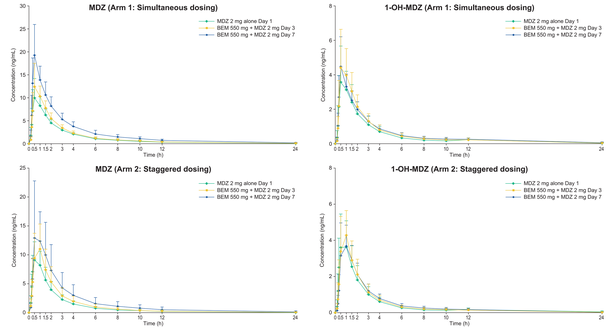
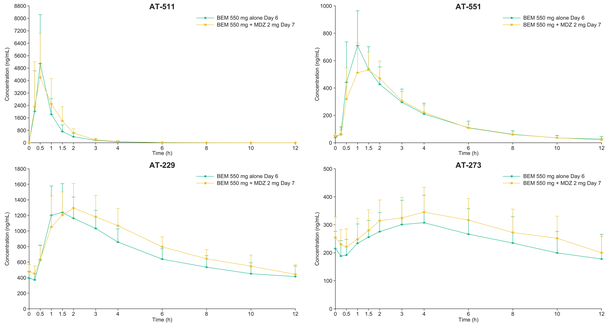


Figure 3. Mean±SD steady-state plasma concentration vs time profiles of BEM and metabolites in the absence and presence of MDZ (Arm 1: Simultaneous dosing)



CONCLUSIONS

- BEM is a weak inhibitor of CYP3A4 (geometric mean ratio [GMR] <2)
- No dose adjustments are needed for drugs that are substrates of CYP3A4 when co-administered with BEM

References

1. Good SS, et al. PLoS One 2020;15:e0227104; 2. Good SS, et al. Antimicrob Agents Chemother 2021;65:e02479–20; 3. Berliba E, et al. Antimicrob Agents Chemother 2019;63:e01201–19; 4. Data on File. Atea Pharmaceuticals; 5. NCT04865445. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04865445 (accessed Feb 2023); 6. 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).

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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, Quebec, Canada, which was contracted to perform this Phase 1 study.

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