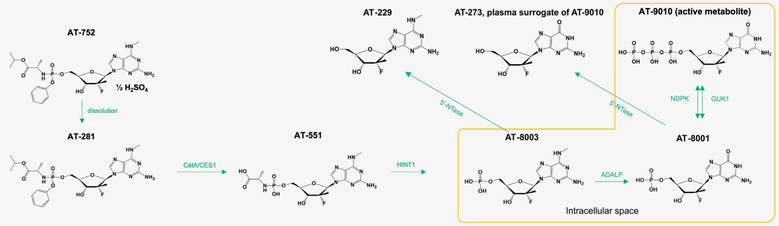
#1358 Safety, tolerability, and pharmacokinetics of AT-752, a novel nucleotide prodrug with pan-serotype activity against dengue virus: results from a Phase 1, first-in-human, dose-escalation study

Xiao-Jian Zhou[1], Jason Lickliter[2], Maureen Montrond[1], Laura Ishak[1], Keith Pietropaolo[1], Dayle James[1], Bruce Belanger[1], Arantxa Horga[1], Janet Hammond[1]
[1]Atea Pharmaceuticals, Boston, MA, United States, [2]Nucleus Network, Melbourne, Australia

BACKGROUND

- Despite the drastic resurgence of dengue virus (DENV) in the last two decades, there are currently no direct-acting antivirals or broadly indicated vaccines available[1]
- AT-752 is a novel guanosine nucleotide prodrug inhibitor of the polymerase of DENV with sub-micromolar, pan-serotype antiviral activity[2]
- AT-752 is readily absorbed and metabolized to the active triphosphate (TP) metabolite AT-9010 in mammalian cells[2–4] **(Figure 1)**

Figure 1. Metabolic pathway of AT-752



- AT-752 is the hemisulfate salt of AT-281, a dual guanosine nucleotide prodrug. AT-281 undergoes multistep metabolic activation to:
  1. AT-551, the L-alanyl intermediate
  2. AT-8003, monophosphate (MP) of the N^6-methyl nucleoside metabolite AT-229
  3. AT-8001, MP of the nucleoside metabolite with the natural guanine base AT-273
  4. AT-9010, the active TP metabolite which potently inhibits the viral RdRp
- AT-8003, AT-8001 or AT-9010 cannot be measured in plasma. Upon dephosphorylation, their nucleoside metabolites AT-229 and AT-273 are formed and enter the general circulation
- Plasma AT-273 is, therefore, considered a surrogate for the intracellular AT-9010

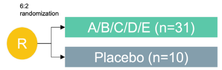
5'-NTase, 5'-nucleotidase; ADALP, adenosine deaminase-like protein; CatA, cathepsin A; CES1, carboxylesterase 1; GUK1, guanylate kinase; HINT1, histidine triad nucleotide binding protein 1; NDPK, nucleoside-diphosphate kinase; RdRp, RNA-dependent RNA polymerase.

- Preclinical evaluation showed good safety and potent efficacy against DENV infection in animal models, prompting this first-in-human (FIH), double-blind, randomized, placebo-controlled study of the safety, tolerability, and pharmacokinetics (PK) of ascending single (Part A) and multiple (Part B) oral doses of AT-752[2,5]

METHODS

- Eligible healthy males and females aged 18–65 years old were sequentially enrolled into Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) cohorts and randomized to receive oral AT-752 or placebo according to the following design **(Figure 2)**

Figure 2. SAD and MAD ascending dose cohorts



Cohort	Dose (mg)	Administration
A	250	Day 1 (fasting)
B (+ food effect)	500	Day 1 (fasting); Day 7 (fed)*
C	1000	Day 1 (fasting)
D (Ethnic)†	1000	Day 1 (fasting)
E	1500	Day 1 (fasting)

Cohort	Dose (mg)	Administration
F	1000	QD x 7 days
G	750	BID x 4 days plus one dose on Day 5
H	750	TID x 4 days plus one dose on Day 5

*As part of the food effect cohort, Cohort B remained confined to the clinic for an additional study drug administration on Day 7 after receiving a high-fat/high-calorie test meal. †Healthy participants of South/Southeast/East Asian origin.
BID, twice a day; QD, once a day; R, randomization; TID, three times a day.

- Plasma and urine samples were collected at pre-determined timepoints/intervals and were quantitated for AT-281 and its metabolites AT-551, AT-229, and AT-273 using validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) methodologies
- PK analyses were performed using non-compartmental approaches
- Safety assessments included adverse events (AEs), standard clinical laboratory tests, vital sign measurements, electrocardiograms (ECGs), and physical examination

RESULTS

Demographics

- Participants were well matched across cohorts in both SAD and MAD cohorts
- Mean age was 28.6 years and 35.3 years in the SAD and MAD cohorts, respectively
- The number of male (51.2%) and female (48.8%) participants in the SAD cohorts were similar whereas the majority were male (62.5%) in the MAD cohorts
- Mean weight was 67.3 kg and 74.7 kg in the SAD and MAD cohorts, respectively
- Most participants were White except for the SAD ethnic cohort where all participants were Asian

Safety/tolerability

- AT-752 was well tolerated; no serious AEs or discontinuations due to AEs occurred **(Table 1)**
- Non-serious AEs were mild or moderate in severity and resolved by the end of the study
- Sporadic cases of gastrointestinal-related events, including mild-to-moderate vomiting, occurred mostly at higher doses
- No trends in clinical laboratory values, vital signs, or ECG parameters were observed

Table 1. AEs reported by >2 subjects

	SAD cohorts								MAD cohorts					
	Pooled placebo n=10	250 mg n=6	500 mg n=7	500 mg fed* n=7	1000 mg n=6	1000 mg ethnic n=6	1500 mg n=6	Total n=41	Pooled placebo n=6	1000 mg QD n=6	750 mg BID n=6	750 mg TID n=6	Total n=24	Overall N=65
Headache	1	0	2	4	1	0	2	8	1	0	1	0	2	10
Nausea	0	0	0	1	1	0	1	3	1	0	1	0	2	5
Vomiting	0	0	0	0	1	0	2	3	0	0	1	0	1	4

*Food effect cohort.

PK evaluation in SAD cohorts

- Upon oral dosing under fasting conditions, the parent prodrug AT-281 was rapidly absorbed and cleared, followed by the appearance of AT-551 which also exhibited a transient exposure. The N^6-methyl nucleoside metabolite AT-229 subsequently peaked and exhibited a slower elimination phase **(Figure 3; Table 2)**
- Plasma AT-273 appeared more gradually and exhibited a long half-life (cohort mean up to 23 hours), reflecting sustained intracellular exposure of the active TP metabolite AT-9010

Figure 3. Mean plasma concentrations vs time profiles of AT-281 and metabolites

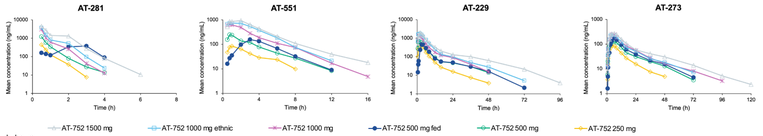


Table 2. Summary of plasma PK parameters of AT-281 and metabolites

AT-281	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng/mL*h)	$t_{1/2}$ (h)	CL_{ss} (L/h)
250 mg	482±131	0.5 (0.5–0.8)	347±64	0.5±0.1	7.5±1.5
500 mg	1230±1110	0.5 (0.5–6.0)	1110±687	0.5±0.1	10.9±5.4
500 mg fed Food effect*	488±303 52.2 (22.1–123.6)	2.0 (0.5–3.0)	980±716 80.2 (38.7–166.2)	0.7±0.3	6.6±1.6
1000 mg	3040±960	0.5 (0.5–0.6)	1910±508	0.5±0.1	11.4±1.7
1000 mg ethnic	3670±1260	0.5 (0.5–0.5)	2730±944	0.5±0.1	9.7±4.2
1500 mg	5050±2080	0.5 (0.5–0.8)	4630±1500	0.6±0.2	8.3±2.2

AT-551	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng/mL*h)	$t_{1/2}$ (h)	CL_{ss} (L/h)
250 mg	89±36	1.0 (0.8–2.0)	302±71	2.1±0.3	2.0±0.3
500 mg	231±155	1.0 (0.8–8.0)	898±437	2.4±0.5	2.1±0.6
500 mg fed Food effect*	154±84 70.5 (42.8–116.0)	3.1 (3.0–4.0)	737±289 78.3 (61.8–99.2)	2.3±0.4	2.1±0.4
1000 mg	695±468	0.8 (0.5–2.0)	2330±1060	2.2±0.4	2.1±0.6
1000 mg ethnic	895±418	0.9 (0.5–2.0)	3320±1630	2.0±0.3	2.1±0.6
1500 mg	1080±217	1.5 (0.8–2.0)	4100±494	3.2±1.2	1.9±0.4

AT-229	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng/mL*h)	$t_{1/2}$ (h)	CL_{ss} (L/h)
250 mg	446±121	2.1 (2.0–3.0)	2890±680	16.9±8.6	13.7±1.6
500 mg	765±307	1.0 (0.8–4.0)	5480±1630	15.1±6.2	13.6±5.4
500 mg fed Food effect*	488±324 64.9 (43.8–96.2)	4.0 (3.0–6.1)	4310±1400 78.4 (68.4–89.9)	11.2±4.9	12.5±2.8
1000 mg	1640±474	0.9 (0.8–3.0)	10300±3070	12.4±10.7	14.2±3.8
1000 mg ethnic	2010±489	1.5 (0.8–2.0)	14000±4210	14.7±10.1	13.4±2.5
1500 mg	2030±600	2.0 (1.0–2.0)	16700±3780	12.5±3.8	15.0±2.4

AT-273	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng/mL*h)	$t_{1/2}$ (h)	CL_{ss} (L/h)
250 mg	91±19	6.0 (3.0–6.0)	1440±280	19.1±10.2	15.8±2.8
500 mg	135±25	4.0 (3.0–8.0)	2390±478	13.9±5.9	16.8±7.6
500 mg fed Food effect*	175±29 132.0 (109.8–158.6)	6.0 (6.0–8.1)	2990±558 125.6 (111.2–141.8)	17.3±11.0	13.4±3.3
1000 mg	241±71	4.1 (4.0–6.3)	4350±1520	26.2±12.2	17.1±6.5
1000 mg ethnic	240±46	5.0 (3.1–6.0)	3830±519	16.3±3.0	18.7±2.1
1500 mg	283±32	6.0 (3.2–6.1)	5460±1190	21.7±6.2	19.5±4.1

*Food effect is represented as geometric mean ratio (90% CI).
C_{max}, AUC_{inf} and $t_{1/2}$ are represented as mean±SD. T_{max} is represented as median (minimum–maximum). CL_{ss} is represented as mean±SD.
AUC_{inf}, area under the curve extrapolated to infinity; CI, confidence interval; CL_{ss}, renal clearance; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, half life; T_{max}, time to reach maximum concentration.

PK ethnic sensitivity

- PK profiles were similar between the South/Southeast/East Asian and mostly Caucasian subject cohorts, suggesting absence of PK ethnic sensitivity; therefore, dose adjustment in these respective populations does not appear necessary

Dose proportionality analysis

- Plasma exposure of AT-281 and its metabolites increased over the studied dose range from 250–1500 mg. AT-229 increased in a dose-proportional manner. AT-281 and AT-551 increased in a greater than dose-proportional manner whereas AT-273 was slightly less than dose-proportional

Food effect

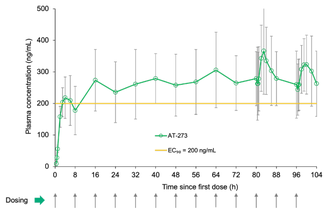
- A high-fat/high-calorie meal delayed and decreased peak level of AT-281, AT-551, and AT-229 but had limited to no impact on their total exposure, and slightly increased the plasma exposure of AT-273 **(Table 2)**
- These results demonstrated that AT-752 can be taken with or without food

Urine excretion

- Following single oral administration of AT-752 at 250 to 1500 mg, urine elimination was low for AT-281 (<3%) and AT-551 (<1%) and was modest for AT-229 (10.7–17.9%) and AT-273 (6.7–8.8%), with total urine recovery ranging from approximately 20–30% across doses
- Renal clearance of the nucleoside metabolites AT-229 and AT-273 exceeded estimated glomerular filtration rate, suggesting involvement of active secretion in their renal elimination

PK evaluation in MAD cohorts

Figure 4. Mean±SD plasma concentrations vs time profiles of AT-273 with AT-752 750 mg TID



- Plasma exposure of AT-273 increased by approximately 25, 60, and 80% with QD, BID, and TID, respectively, due to its long plasma half-life, reflective of rapid accumulation and sustained intracellular exposure of the active metabolite AT-9010
- The 750 mg TID dose led to a rapid increase in plasma AT-273 levels, exceeding the 90% effective concentration (EC_{90}) of the drug in inhibiting DENV replication in vitro (0.64 µM or 200 ng/mL of eq. AT-273) and maintained such levels over the treatment period **(Figure 4)**

Table 3. Summary of steady-state plasma PK parameters of AT-281 and metabolites

AT-281	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng/mL*h)
1000 mg QD (Day 7)	3810±1670	0.5 (0.5–0.5)	3090±1530
750 mg BID (Day 5)	3490±1280	0.5 (0.5–0.8)	2690±640
750 mg TID (Day 5)	3010±754	0.5 (0.5–1.0)	2540±572

AT-551	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng/mL*h)
1000 mg QD (Day 7)	392±143	1.0 (0.8–2.0)	1650±498
750 mg BID (Day 5)	365±159	1.0 (0.8–2.0)	1330±503
750 mg TID (Day 5)	245±30	1.5 (0.8–2.0)	944±173

AT-229	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng/mL*h)
1000 mg QD (Day 7)	1200±284	0.9 (0.8–2.0)	8290±2290
750 mg BID (Day 5)	1470±404	1.5 (0.8–2.2)	7960±2970
750 mg TID (Day 5)	1600±640	1.5 (1.0–2.0)	8880±3330

AT-273	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng/mL*h)
1000 mg QD (Day 7)	241±56	4.0 (3.0–4.0)	3120±694
750 mg BID (Day 5)	288±58	3.5 (3.0–4.0)	2680±730
750 mg TID (Day 5)	330±98	3.5 (3.0–6.0)	2370±743

C_{max} and AUC_{tau} represented as mean±SD. T_{max} is represented as median (minimum–maximum).
AUC_{tau}, area under plasma concentration-time curve over dosing interval.

CONCLUSIONS

- AT-752 was safe and well tolerated when administered as a single oral dose up to 1500 mg, or when administered as multiple oral doses up to 750 mg TID
- AT-752 exhibited no PK ethnic sensitivity in South/Southeast/East Asian participants and no food effect was seen
- The overall safety and PK results obtained in this FIH study supported the initiation of two clinical studies of AT-752 for the treatment and prophylaxis of DENV infection[6,7]

References
1. World Health Organization (WHO). Dengue and severe dengue. June 2020; 3. Good SS et al. Antimicrob Agents Chemother 2021;65(11):e0098821; 3. Good SS et al. PLoS One 2020;15(1):e0227104; 4. Good SS et al. Antimicrob Agents Chemother 2021;65(4):e02479–20; 5. NCT04722627. ClinicalTrials.gov; 6. NCT05466240. ClinicalTrials.gov; 7. NCT05366439. ClinicalTrials.gov.

Acknowledgements
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, Laura Ishak, Keith Pietropaolo, Dayle James, Bruce Belanger, Arantxa Horga, Janet Hammond are employees of and may own stock in Atea Pharmaceuticals, Boston, MA, USA; Jason Lickliter is an employee of Nucleus Network, Melbourne, Australia, which was contracted to help perform this research.

Poster #1358 presented at American Society of Tropical Medicine & Hygiene (ASTMH) 2022 Annual Meeting 30 October – 3 November in Seattle, USA