AT-752, A Novel Nucleotide Prodrug With Pan-Serotype Activity Against Dengue Virus, Does Not Affect Cardiac Repolarization: Results From a Robust QT/QTc Evaluation in Healthy Participants

P2941

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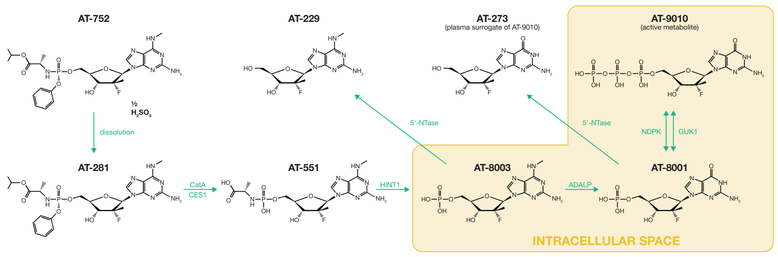
BACKGROUND

- Despite a drastic resurgence of dengue virus in the last two decades, there are currently no direct-acting antivirals or broadly indicated vaccines available[1]
- AT-752 is an oral double prodrug of a guanosine nucleotide analog with potent inhibitory activity against flaviviruses[2]
- AT-752 is readily absorbed and metabolized to the active triphosphate metabolite AT-9010 in mammalian cells[2,3] **(Figure 1)**
- In a Phase 1, first-in-human, single (SAD) and multiple ascending dose (MAD) study (NCT04722627), AT-752 was well tolerated after single or multiple oral doses in healthy participants[4,5]
- Here, we report results of concentration-QTc (C-QTc) analysis as part of the above dose-escalation study

Figure 1. Metabolic pathway of AT-752[2,3,6,7]



- AT-752 is the hemisulfate salt of AT-281, a dual-nucleotide prodrug[2]
- AT-281 undergoes multistep metabolic activation to:[2,3]
  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 triphosphate metabolite which potently inhibits the viral RdRp
- AT-8003, AT-8001, or AT-9010 are not measurable in plasma.[6] Upon dephosphorylation, their nucleoside metabolites AT-229 and AT-273 are formed and enter the general circulation[3,6,7]
- Plasma AT-273 is, therefore, considered a surrogate for the intracellular AT-9010[6,7]

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.

METHODS

Study design

- Eligible, healthy participants 18–65 years of age were sequentially enrolled into SAD and MAD cohorts and randomized to receive AT-752 or placebo according to the following design **(Figure 2)**

Figure 2. SAD and MAD 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 × 7 days
G	750	BID × 4 days plus one dose on Day 5
H	750	TID × 4 days plus one dose on Day 5

*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 daily.

Cardiac safety assessment

- Continuous 12-lead electrocardiograms (ECGs) were recorded pre and post dose, and extracted at PK-matched timepoints
- ECG intervals were measured in a blinded manner using the Early Precision QT technique
  - At each nominal timepoint specified, up to 10 ECG replicates were extracted
  - Categorical T-wave morphology analysis and measurement of PR (time between atrial depolarization and ventricular depolarization) and QRS (ventricular depolarization) intervals were performed using a semi-automated process in three of the 10 ECG replicates at each timepoint
- The primary ECG objective was to evaluate the effect of single and multiple ascending AT-752 doses on the QT interval corrected for heart rate (HR) using the Fridericia formula (QTcF) using C-QTc analysis

RESULTS

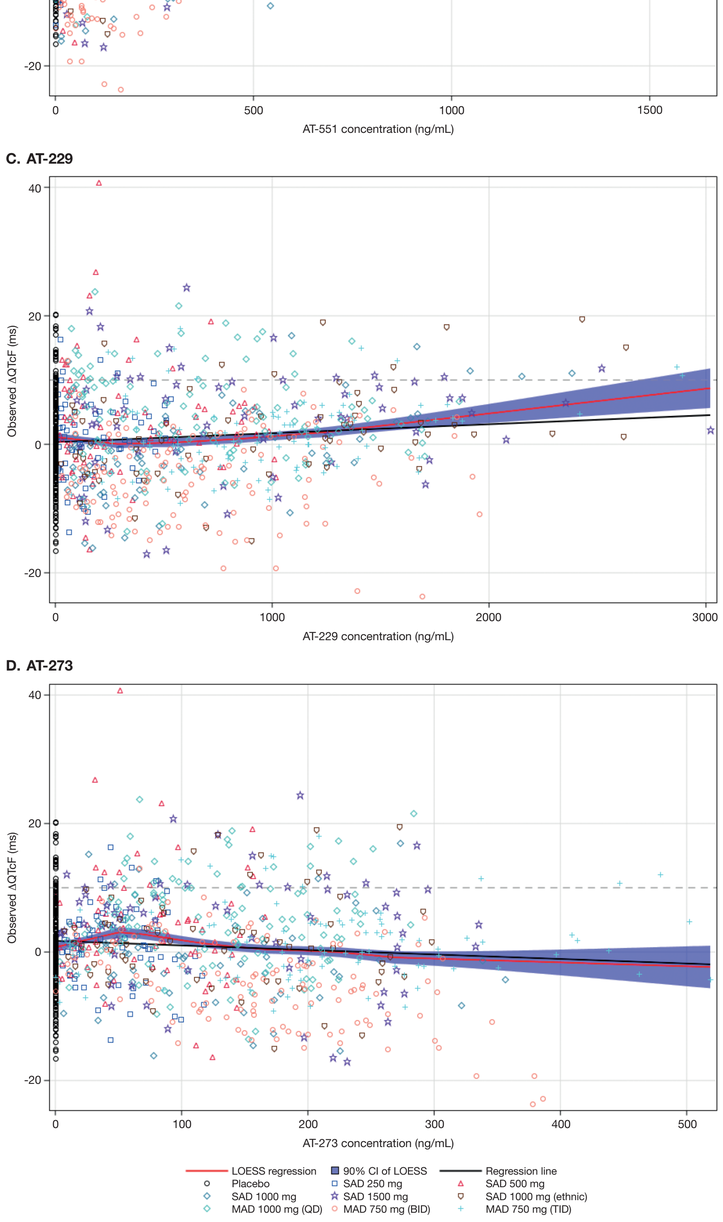
Effect on HR

- AT-752 at the studied doses (up to 1500 mg single dose, and 750 mg TID x 4.5 days) did not have a clinically relevant effect on HR
- Changes from baseline in HR of participants who received AT-752 generally followed the pattern observed in those who received placebo, with no apparent dose dependency

Effect on cardiac repolarization: the QT interval

- Changes from baseline in QTcF (ΔQTcF) with AT-752 treatment generally followed the placebo pattern across post-dose timepoints in the SAD and MAD cohorts
- A linear mixed-effects model was selected to fit to the ΔQTcF vs plasma concentration of AT-281 (the freebase of AT-752), the L-alanyl intermediate AT-551, and the two nucleoside metabolites AT-229 and AT-273 **(Figure 3)**
- For the pooled SAD and MAD data, a full model including all analytes was initially fitted and the model with AT-551 alone (resulting in the lowest AIC value) was selected as the primary model **(Table 1)**
- The estimated slope of AT-551 C-QTc relationship was shallow and statistically significant, with a small and statistically insignificant treatment effect-specific intercept **(Figure 4)**
- At the geometric mean of the maximum plasma concentration (C_{max}), the effect on placebo-corrected ΔQTcF (ΔΔQTcF) was predicted to be 4.42 ms (90% CI: 1.50–7.34) for AT-752 1500 mg, the highest single dose tested, and 0.66 ms (90% CI: -1.56–2.89) for the 750 mg TID dose, the highest daily total repeat dose tested, all below 10 ms **(Table 2)**
  - AT-752 and its metabolites did not cause any clinically relevant QTc prolongation within their observed plasma concentrations of up to 8.1, 1.5, 3.0, and 0.52 µg/mL for AT-281, AT-551, AT-229, and AT-273, respectively

Figure 3. Scatter plots of ΔQTcF vs plasma concentrations of AT-281 and metabolites with simple linear regression and LOESS regression (Pooled Part A and Part B)



The red line with the blue shaded area denotes the LOESS regression and 90% confidence limits. The black solid line denotes the simple linear regression line. The plotted points denote the pairs of observed AT-281/AT-551/AT-229/AT-273 plasma concentrations and ΔQTcF.
CI, confidence interval; LOESS, locally weighted scatter plot smoothing; MAD, multiple ascending dose; SAD, single ascending dose; ΔQTcF, change from baseline in corrected QT interval using Fridericia's formula.

Table 1. AIC values for all models from C-QTc analysis (Pooled Part A and Part B)

Model	AT-281/metabolites included in model	AIC value	Treatment effect ms (t-value)	AT-281 ng/mL (p-value)	AT-551 ng/mL (p-value)	AT-229 ng/mL (p-value)	AT-273 ng/mL (p-value)
A	AT-281/all metabolites	5694.6	1.46 (1.09)	-0.000535 (0.1077)	0.0058 (0.0075)	-0.000268 (0.7993)	-0.0132 (0.0087)
B	AT-281 + AT-551 + AT-273	5682.8	1.43 (1.07)	-0.000518 (0.1115)	0.0053 (<0.0001)		-0.0137 (0.0025)
C	AT-551 + AT-273	5671.1	1.05 (0.80)		0.0045 (0.0003)		-0.0113 (0.0082)
D	AT-281	5685.6	0.47 (0.39)	0.00029 (0.3128)			
E	AT-551	5669.0	-0.45 (-0.38)		0.0047 (0.0001)		
F	AT-229	5681.5	-0.19 (-0.15)			0.0012 (0.0601)	
G	AT-273	5672.4	2.24 (1.71)				-0.0127 (0.0031)

AIC, Akaike Information Criterion.

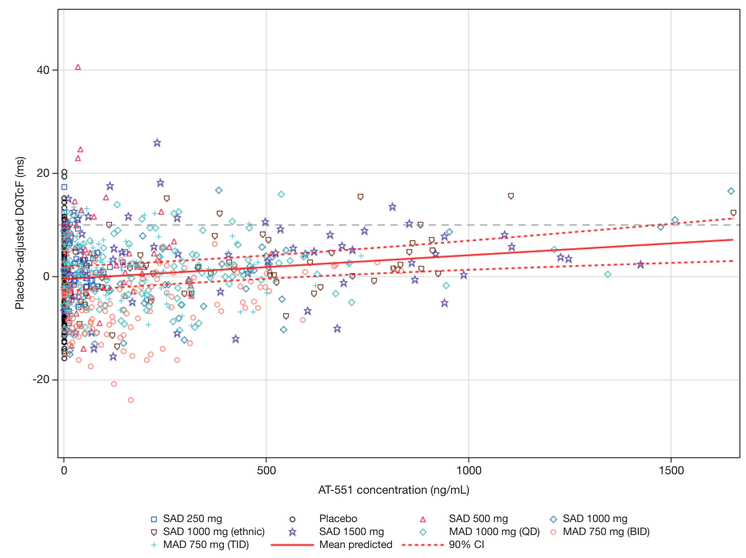
Table 2. Predicted ΔΔQTcF interval at geometric mean peak concentrations for AT-551 (Model E; Pooled Part A and Part B)

Treatment	Geometric mean, ng/mL C_{max} of AT-551	ΔΔQTcF estimate, ms (90% CI)
SAD 250 mg	84.0	-0.07 (-2.37, 2.24)
SAD 500 mg	181.8	0.38 (-1.87, 2.63)
SAD 1000 mg	613.5	2.37 (0.04, 4.69)
SAD 1000 mg (ethnic)	820.8	3.32 (0.77, 5.87)
SAD 1500 mg	1061.0	4.42 (1.50, 7.34)
MAD 1000 mg QD	333.6	1.08 (-1.13, 3.29)
MAD 750 mg BID	336.2	1.09 (-1.12, 3.30)
MAD 750 mg TID	242.9	0.66 (-1.56, 2.89)
10 ms threshold	1467	6.29 (2.57, 10.00)

Based on a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched AT-551 plasma concentration as an explanatory variate, centered baseline QTcF as an additional covariate, treatment (active=1 or placebo=0) and time as fixed effects, and a random intercept and slope per subject.
C_{max}, maximum plasma concentration; QTcF, corrected QT interval using Fridericia's formula; ΔΔQTcF, placebo-adjusted ΔQTcF.

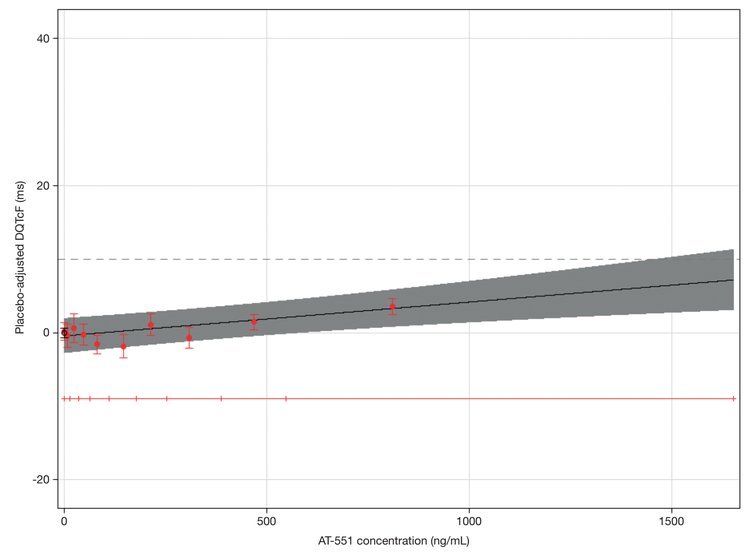
Figure 4. Primary C-QTc model (Model E; Pooled Part A and Part B)

A. Scatter plot of estimated placebo-adjusted QTcF and observed AT-551 plasma concentrations



The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = −0.45 (ms) + 0.0046 (ms per ng/mL) × AT-551 plasma concentration (ng/mL). The plotted points denote the pairs of observed drug plasma concentrations and estimated placebo-adjusted ΔQTcF (ΔΔQTcF) by subjects for each active dose group and placebo group. The individually estimated placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) equals the individual $\Delta QTcF_{i,k}$ for subject i administered with active drug or placebo at timepoint k minus the estimation of the time effect at timepoint k.

B. Model-predicted ΔΔQTcF and estimated ΔΔQTcF across deciles of AT-551 plasma concentrations



The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = −0.45 (ms) + 0.0046 (ms per ng/mL) × AT-551 plasma concentration (ng/mL). The red filled circles with vertical bars denote the estimated mean ΔΔQTcF with 90% CI displayed at the associated median plasma concentration within each decile for AT-551, among which the individually estimated placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) equals the individual $\Delta QTcF_{i,k}$ for subject i administered with AT-551 at time point k minus the estimation of time effect at time point k. The black circle with vertical bars denotes the mean placebo-adjusted ΔQTcF with 90% CI for placebo at a concentration of 0. The horizontal red line with notches shows the range of concentrations divided into deciles for AT-551. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10-20% of the data and so on.

Effect on cardiac conduction: the PR and QRS intervals

- AT-752 at the studied doses did not have a clinically relevant effect on cardiac conduction i.e., the PR and QRS intervals. Changes from baseline in these measures with AT-752 treatment followed the pattern observed in participants who received placebo

Categorical outliers and morphology analyses

- In the AT-752 treatment arms, one tachycardic outlier was identified among the SAD cohorts (Part A); no tachycardic or bradycardic outliers were identified among the MAD cohorts (Part B) **(Table 3)**
- One participant had a treatment-emergent QTcF value >450 and ≤480 ms, and one participant had a ΔQTcF increase >30 ms and ≤60 ms in the SAD part of the study
- No participants in the MAD cohort had a treatment-emergent QTcF value of >450 or ΔQTcF increase >30 ms
- No PR or QRS outliers, treatment-emergent T-wave morphology changes or U waves with AT-752 treatment (SAD or MAD) were observed

Table 3. Categorical outliers and treatment-emergent ECG morphology occurring in ≥1 participant

SAD cohorts (Part A)	AT-752 250 mg	AT-752 500 mg	AT-752 500 mg (fed)	AT-752 1000 mg	AT-752 1000 mg (ethnic)	AT-752 1500 mg	Pooled placebo	Placebo (fed)
Total, n	6	7	6	6	6	6	10	2
HR tachycardic outliers, n (%)	0	0	0	1 (16.7)	0	0	0	0
QTcF new >450 and ≤480 ms, n (%)	-	1 (14.3)	0	0	0	0	0	0
ΔQTcF >30 and ≤60 ms, n (%)	-	1 (14.3)	0	0	0	0	0	0

MAD cohorts (Part B)	AT-752 1000 mg QD	AT-752 750 mg BID	AT-752 750 mg TID	Pooled placebo
Total, n	6	6	6	6
QTcF new >450 and ≤480 ms, n (%)	0	0	0	1 (16.7)

CONCLUSIONS

- AT-752 had no clinically relevant effects on cardiac repolarization, heart rate, PR interval, or QRS duration
- A QTc effect exceeding 10 ms is unlikely across the full observed plasma concentration ranges of AT-281 and metabolites

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Disclosures

Xiao-Jian Zhou, Maureen Montrond, Keith Pietropaolo, Bruce Belanger, Arantxa Horga, and Janet Hammond are employees of and may own stock in Atea Pharmaceuticals, Boston, MA, USA. Todd Rudo and Hongqi Xue are employees of Clario, USA, which was contracted to perform this analysis.

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