Despite a drastic resurgence of dengue virus in the last two decades, AT-281 undergoes multistep metabolic activation to:2,3

Here, we report results of C-QTc analysis as part of the AT-752 at the studied doses did not have a clinically relevant effect on cardiac repolarization: the QT interval corrected for heart rate (HR) (Figure 4). O

Effect on cardiac repolarization: the QT interval corrected for heart rate (HR)

Cardiac safety assessment

Continuous 12-lead electrocardiograms (ECGs) were recorded pre and post dose, and collected at PK-matched timepoints.

ECG intervals were measured in a blinded manner using the Early Precision QT technique.

– At each nominal timepoint, 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 (ΔΔQTcF) 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 days) did not have a clinically relevant effect on HR.

Changes from baseline in HR of participants who received AT-752 were generally followed the pattern observed in those who received placebo, with no apparent dose dependency.

Effect on cardiac repolarization: the QT interval corrected for heart rate

– Changes from baseline in ΔΔQTcF (ΔΔQTc) 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 ΔΔQTcF vs plasma concentrations of AT-281 (the freebase of the SAD-2, the L-aryl intermediate AT-551, and the two nucleoside metabolites AT-229 and AT-273 (Figure 5). 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 (ΔΔQTcF) using C-QTC analysis

AIC values for all models from C-QTC analysis

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Included in model</th>
<th>ΔAIC</th>
<th>ΔAIC (t-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AT-281 (total)</td>
<td>144.3 0.00 (0.00, 0.23)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>B</td>
<td>AT-551</td>
<td>144.9 0.67 (0.00, 1.34)</td>
<td>0.67 (0.11)</td>
</tr>
<tr>
<td>C</td>
<td>AT-229</td>
<td>145.3 1.09 (0.00, 2.18)</td>
<td>1.09 (&lt;0.0001)</td>
</tr>
<tr>
<td>D</td>
<td>AT-273</td>
<td>145.3 1.09 (0.00, 2.18)</td>
<td>1.09 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

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

References


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Disclosures

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