**Key Takeaways**

- This thorough QT/corrected QT (QTC) study evaluated the effect of the next-generation HIV-1 maturation inhibitor GSK3640254 (GSK’254) on cardiac repolarization in healthy participants.
- At exposures associated with a potential therapeutic dose of GSK’254, no clinically relevant effects on QTc prolongation, heart rate, or cardiac conduction were observed and no safety or tolerability events occurred, supporting the continued clinical development of GSK’254.
- At supratherapeutic GSK’254 exposures, the upper bound of the 90% CI for QTc prolongation exceeded the clinically relevant 10-ms threshold.

**Introduction**

GSK’254 is a next-generation HIV-1 maturation inhibitor with PK supporting once-daily (QD) therapy for HIV-1 treatment.

In preclinical studies, minimal QT effects were observed in 1 dog administered a single dose of GSK’254 17 mg/kg up to a maximum concentration of 7960 ng/mL.

In previous clinical studies, 1 healthy participant receiving GSK’254 200 mg reported an adverse event (AE) of isolated and limited palpitations without changes on electrocardiogram.

In this 2-part, randomized, thorough QT/QTC study, the effect of GSK’254 on cardiac repolarization was evaluated in healthy adults.

**Methods**

**Part 1: Sentinel Cohort**

- 50 participants enrolled, 8/8 (100%) in part 1 and 40/42 (95%) in part 2 completed the study.
- 2 participants withdrew from the study in part 2 due to an AE (coronavirus infection) and pregnancy.
- In parts 1 and 2, 35 (70%) participants were male, 21 (42%) were White/Caucasian/European heritage, and 20 (40%) were Black/African American; mean age was 34 years.

**Part 2: Main QTC Study**

- On Day 7 in part 2, geometric mean (95% CI) GSK’254 maximum concentrations (Cmax) were observed 5 hours post-dose with GSK’254 dosing (100 mg: 830 [738, 934] ng/mL; 500 mg: 4260 [3750, 4840] ng/mL).
- Estimated population slope of the cQT model was 0.0025 ms per ng/mL (90% CI, 0.0020, 0.0030).
- Least squares (LS) mean ΔΔQTcF for GSK’254 100 mg followed the placebo pattern across time points, with a maximum LS mean ΔΔQTcF of 1.7 ms.
- The upper bound of the 90% CI remained <10 ms through 24 hours post-dose.
- Maximum LS mean ΔΔQTcF for GSK’254 500 mg exceeded the 10 ms threshold at 4.5 hours post-dose: 10.6 ms (90% CI, 7.75, 13.38).
- The most common AE was diarrhea, reported in 7 participants in part 2 (n=1 during treatment with placebo).
- Abdominal pain, nausea, medical device site dermatis, vesical puncture site pain, acne, and maculopapular rash were reported in 2 participants each in part 2.
- All other AEs were reported by 1 participant each in either part 1 or part 2.

**Assessments and Analyses**

- In each treatment period, electrocardiograms were extracted in triplicate before dosing on Day 1 and 24 hours post-dose on Day 7 of each treatment period.
- Assessments included heart rate, PR interval, QRS interval, and QT interval corrected using Fridericia’s formula (QTcF).
- Concentration-QTC (cQT) analyses modeled the relationship between individually observed GSK’254 plasma concentrations and placebo-adjusted change from baseline in QTcF (ΔΔQTcF).
- PK parameters were calculated by standard noncompartmental analysis.
- Safety assessments included monitoring of AEs.

**Results**

**Participants**

- Of 50 participants enrolled, 8/8 (100%) in part 1 and 40/42 (95%) in part 2 completed the study.
- 2 participants withdrew from the study in part 2 due to an AE (coronavirus infection) and pregnancy.
- In parts 1 and 2, 35 (70%) participants were male, 21 (42%) were White/Caucasian/European heritage, and 20 (40%) were Black/African American; mean age was 34 years.

**Main QTC Study Findings**

- On Day 7 in part 2, geometric mean (95% CI) GSK’254 maximum concentrations (Cmax) were observed 5 hours post-dose with GSK’254 dosing (100 mg: 830 [738, 934] ng/mL; 500 mg: 4260 [3750, 4840] ng/mL).
- Estimated population slope of the cQT model was 0.0025 ms per ng/mL (90% CI, 0.0020, 0.0030; P=0.001), with a treatment effect-specific intercept of 0.61 ms (90% CI, –0.083, 1.253; P=0.1216; Figure 1).
- Least squares (LS) mean ΔΔQTcF for GSK’254 100 mg followed the placebo pattern across time points, with a maximum LS mean ΔΔQTcF of 1.7 ms.
- The upper bound of the 90% CI remained <10 ms through 24 hours post-dose.
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**Table. Predicted ΔΔQTcF Interval at Geometric Mean GSK’254 Cmax**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Geometric mean GSK’254 Cmax, ng/mL</th>
<th>ΔΔQTcF estimate (90% CI), ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK’254 100 mg</td>
<td>830.3</td>
<td>2.72 (2.04, 3.39)</td>
</tr>
<tr>
<td>GSK’254 500 mg</td>
<td>4283.5</td>
<td>11.49 (9.24, 13.73)</td>
</tr>
<tr>
<td>10-ms threshold</td>
<td>3070</td>
<td>8.40 (6.79, 10.02)</td>
</tr>
</tbody>
</table>

**Figure 2. Model-Predicted Mean (95% CI) ΔΔQTcF at Geometric Mean Peak GSK’254 Concentrations Associated With 100- and 500-mg Doses**

**Figure 1. Goodness-of-Fit Plot of the cQT Model**

**Safety**

- AEs were reported by 3/8 (38%) participants in part 1 and 18/42 (43%) in part 2, all of which were maximum grade 1.