Effects of the HIV-1 Maturation Inhibitor GSK3640254 on QT Interval in Healthy Participants

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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[1]
- 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[1]
- 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

- In part 1, healthy participants were randomized 3:1 to receive GSK'254 500 mg or placebo QD for 7 days to determine safety and PK of a 500-mg GSK'254 supratherapeutic dose
  - All doses were administered with a moderate-fat meal

Part 2: Main QTc Study

- In part 2, healthy participants were randomized to 12 treatment sequences, each composed of 4 sequential 7-day treatment periods:
  - GSK'254 100 mg QD (potential therapeutic dose)
  - GSK'254 500 mg QD (supratherapeutic dose)
  - Placebo QD for 7 days
  - Placebo QD for 6 days and a single dose of moxifloxacin 400 mg on Day 7
- Each treatment period was followed by a ≥7-day washout
- All treatments were administered with a moderate-fat meal

Assessments and Analyses

- In each treatment period, electrocardiograms were extracted in triplicate before dosing on Day 1 and pre-dose and through 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

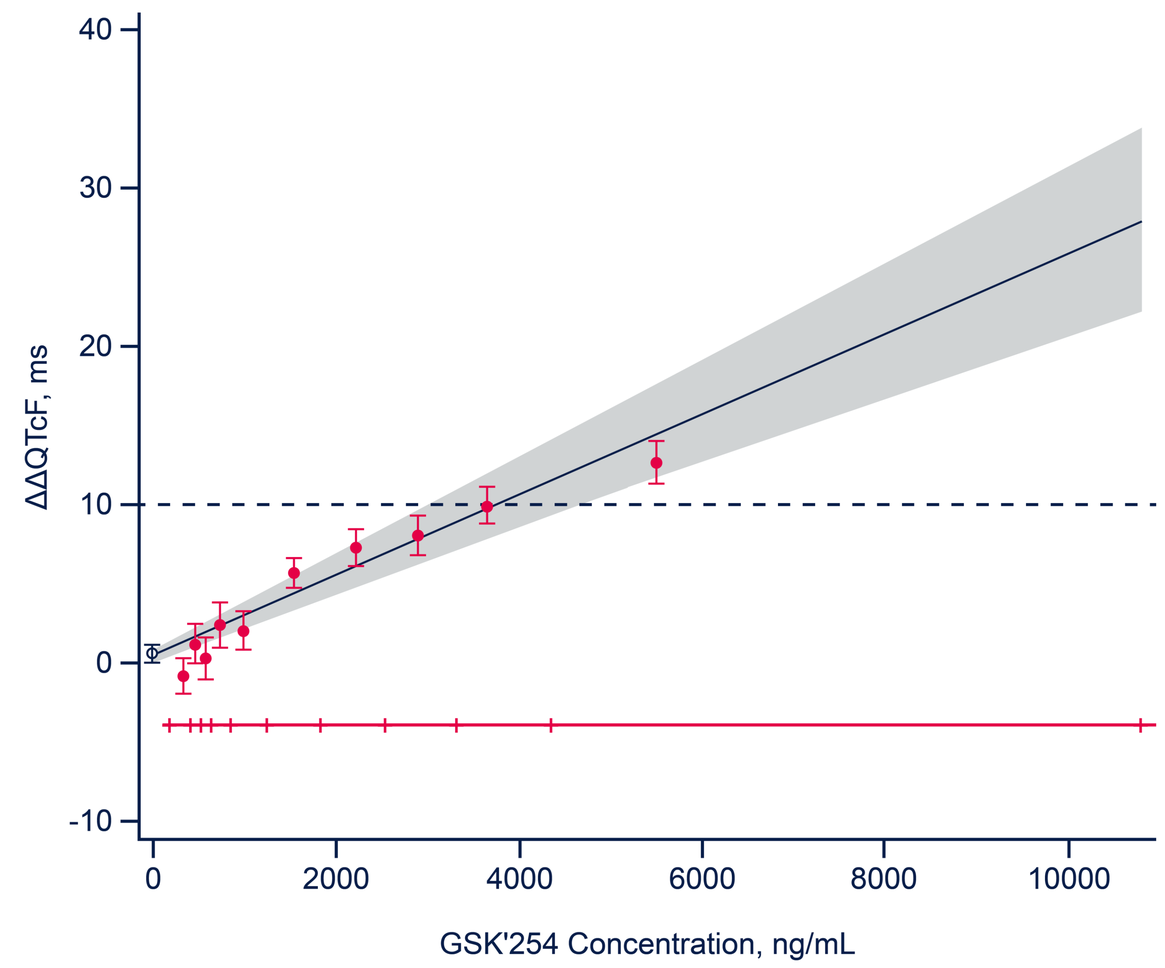
Participants

- 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 (C_{max}) 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, 0.00200, 0.00308; *P*<0.0001), with a treatment effect–specific intercept of 0.61 ms (90% CI, −0.038, 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
- 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 upper bound of the 90% CI for ΔΔQTcF is expected to remain <10 ms at GSK'254 plasma concentrations <3070 ng/mL (Table; Figure 2)
- Neither GSK'254 dose had clinically relevant effects on heart rate or cardiac conduction (ie, PR and QRS intervals)

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



ΔΔQTcF, placebo-adjusted change from baseline in QT interval corrected using Fridericia's formula. The solid blue line and gray shaded region denote the model-predicted mean (90% CI) ΔΔQTcF as a function of GSK'254 concentration. The red filled circles with error bars denote the estimated mean ΔΔQTcF with 90% CI at the associated median plasma concentration within each GSK'254 concentration decile. The blue open circle with error bars denotes the mean ΔΔQTcF with 90% CI for placebo. The horizontal red line with notches shows the range of GSK'254 concentrations divided into deciles. The blue dashed line denotes the 10-ms threshold.

Safety

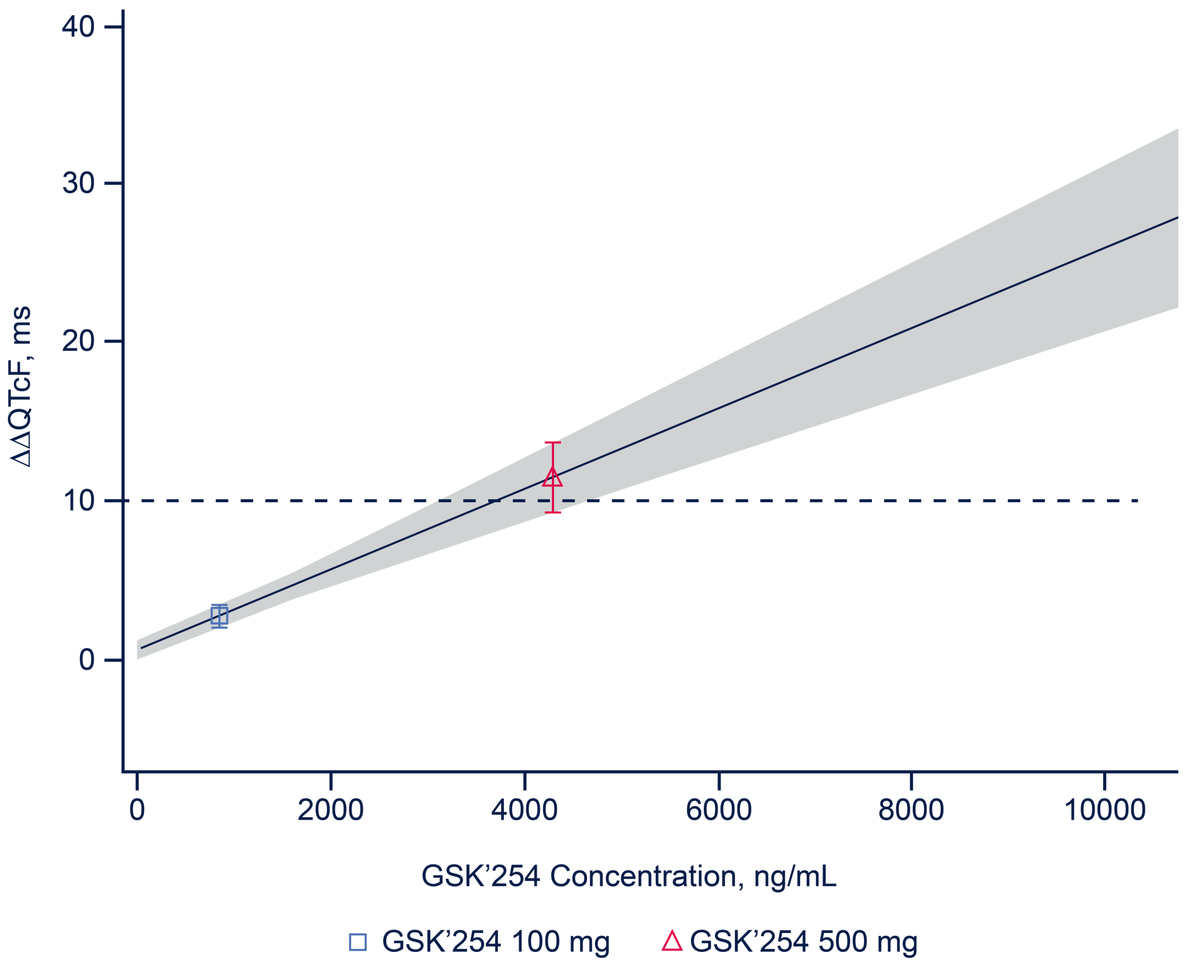
- AEs were reported by 3/8 (38%) participants in part 1 and 18/42 (43%) in part 2, all of which were maximum grade 1
- The most common AE was diarrhea, reported in 7 participants in part 2 (n=1 during treatment with placebo; n=6 during treatment with GSK'254 500 mg)
  - Abdominal pain, nausea, medical device site dermatitis, vessel 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

Table. Predicted ΔΔQTcF Interval at Geometric Mean GSK'254 C_{max}

Treatment	Geometric mean GSK'254 C_{max}, ng/mL	ΔΔQTcF estimate (90% CI), ms
GSK'254 100 mg	830.3	2.72 (2.04, 3.39)
GSK'254 500 mg	4283.5	11.49 (9.24, 13.73)
10-ms threshold	3070	8.40 (6.79, 10.02)

C_{max}, maximum concentration; ΔΔQTcF, placebo-adjusted change from baseline in QT interval corrected using Fridericia's formula. Based on a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched GSK'254 plasma concentration as a fixed effect, centered baseline QTcF as an additional covariate, treatment (active = 1 or placebo = 0) and time as categorical factors, and a random intercept and slope per participant.

Figure 2. Model-Predicted Mean (90% CI) ΔΔQTcF at Geometric Mean Peak GSK'254 Concentrations Associated With 100- and 500-mg Doses



ΔΔQTcF, placebo-adjusted change from baseline in QT interval corrected using Fridericia's formula. The solid blue line and gray shaded region denote the model-predicted mean (90% CI) ΔΔQTcF as a function of GSK'254 concentration. The points plotted denote the estimated mean (90%) ΔΔQTcF at geometric mean GSK'254 C_{max}. The blue dashed line denotes the 10-ms threshold.

Conclusions

- No clinically relevant effects on QTc prolongation, heart rate, or cardiac conduction were seen in healthy participants at concentrations associated with projected therapeutic GSK'254 doses being evaluated in phase IIb studies (100-200 mg)
- These results support continued clinical development of GSK'254 for HIV-1 treatment

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Reference: 1. Joshi et al. *Pharmacol Res Perspect*. 2020;8:e00671.

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