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RESPONSE LETTER TO THE EDITOR

Response Letter to the Editor: "Assumption Checking Before Application of the Prespecified QT Linear Mixed Effect Model is Essential"

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To the Editor:
In the Letter to the Editor regarding: "Assumption checking is essential," the authors questioned satisfaction of assumptions required for applying the prespecified linear mixed effect (LME) model, and our conclusion on reconsidering the LME model when drug-induced circadian rhythm change is expected.[1] We appreciate the authors' investigation of exploratory plots. We believe the basic assumptions are met in part (i) and consideration of exploring alternative models based on known pharmacology is warranted in part (ii) because exploratory plots may not be sensitive to identify all characteristics of drug effects on QT.

Regarding part (i), we believe assumptions were satisfied for the following reasons:

1. We previously investigated concentration – heart rate (HR) LME model and confirmed ΔΔHR (90% confidence interval (CI)) estimate at the highest dose steady-state maximum concentration (C_{max}) was 3.13 (1.85–4.42) bpm, which would not meaningfully impact Fridericia corrected QT (QTcF) assessment. **Figure S1b** also showed no meaningful relationship between QTcF and risk ratio interval.[1]
2. Given the large variability in ΔΔQTcF, hysteresis also cannot be ruled in. The 90% CIs substantially overlapped across the majority of time points (**Figure 1a**).
3. The concentration-ΔQTcF relationship may be influenced by several observations at low concentrations, which is confounded by circadian rhythm variation. Even with assuming a nonlinear relationship, the maximum change is approximately 4 ms. Therefore, the LME model represents a conservative approach.
4. We discussed similarities between studies in the Methods section. Investigation of electrocardiogram (ECG) acquisition procedures revealed nothing to suspect meaningful differences should exist.

Hysteresis plot of simulation data, where "truth" is no hysteresis, were additionally investigated in part (ii) (**Figure 1b**). This could be interpreted as counterclockwise hysteresis, even though none exists. Given the possible conflicting

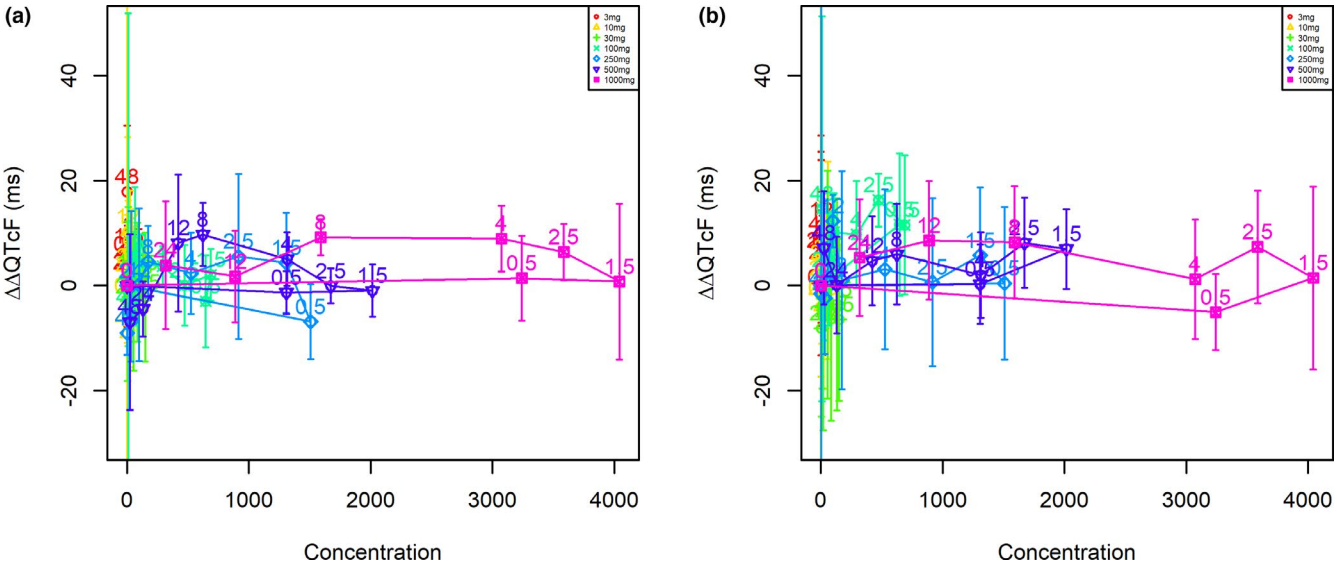

Figure 1 Mean placebo corrected QTcF interval change from baseline (ΔΔQTcF) and concentration plot connected in temporal order by dose for (**a**), observed PF-05251749 data and (**b**), simulated data for the scenario of no QT prolongation in the absence of circadian rhythm change.

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interpretation of graphical analyses, further work is needed to develop definitive criteria for hysteresis checking.

Regarding part (ii), we investigated exploratory plots for randomly sampled simulation datasets in the worst scenario (1.2-fold period lengthening). Because only QTcF was simulated, HR-related plots were not examined. As seen in **Figure S5,** basic assumptions were met, and the LME model would be deemed acceptable. However, because drug-induced circadian rhythm change cannot be identified in the current set of plots but can significantly affect ΔΔQTcF inference, additional modeling should be undertaken given the known pharmacology.

We acknowledge that basic assumption checking should be satisfied before applying a LME model. Given the highly variable nature of QT data, graphical analysis may not always be sensitive to identify all characteristics of drug effects on QT. Drug-induced circadian rhythm change may be one case misinformed by graphical analysis alone.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

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1. Huh, Y., Chen, D., Riley, S., Chang, C. & Nicholas, T. Evaluation of QT liability for PF-05251749 in the presence of potential circadian rhythm modification. *CPT Pharmacometrics Syst. Pharmacol.* **9**, 60–69 (2020).