

# Evaluation of Darigabat QTc Prolongation in Healthy Volunteers: a Concentration-QTcF Analysis

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## Introduction

- Darigabat (also CVL-865; formerly PF06372865) is a positive allosteric modulator (PAM) that selectively enhances the effect of GABA at  $\alpha 2/ \alpha 3/ \alpha 5$  subunits while sparing activity at  $\alpha 1$ 
  - Potential treatment for focal onset epilepsy and anxiety-related disorders
- Single (0.04-100 mg) and multiple (2.5-42.5 BID) oral doses previously investigated in healthy volunteers [1-3]
  - Favourable safety and pharmacodynamic profile
  - No dose-dependent QTcF prolongation or changes in heart rate up to 100 mg

## Aim

Further evaluation of the cardiodynamic effects of darigabat with a concentration-QTcF analysis

## Results

### Assumptions: effect on heart rate and adequacy of Fredericia correction

- No effect of darigabat on heart rate (Figure 1A)
- Significant relationship between QTcF and RR interval in the active treatment group (Figure 1B)
  - increased risk of false positive QTcF prolongation

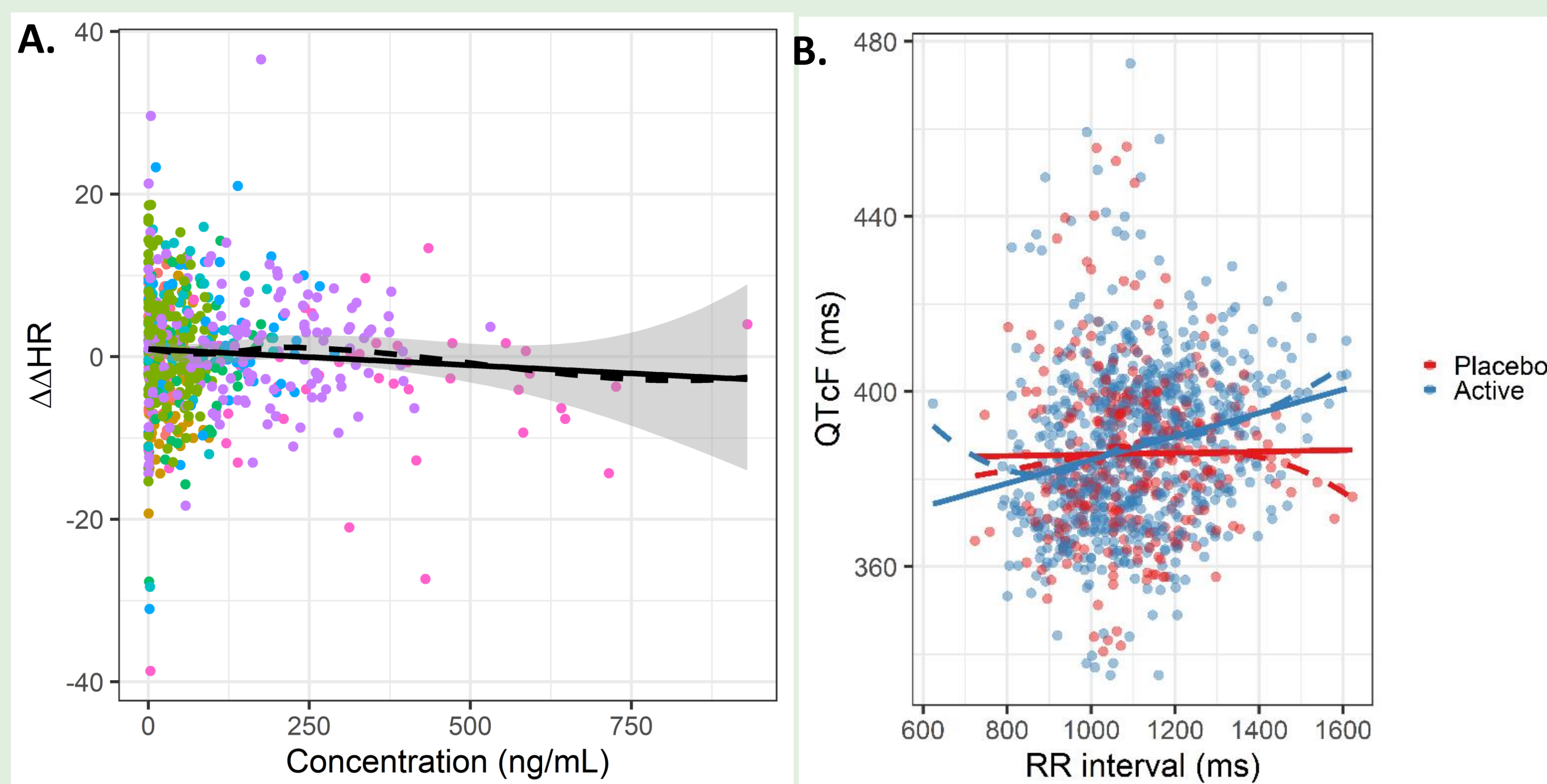


Figure 1. Scatter plot of  $\Delta\Delta HR$  vs Darigabat concentrations (A) and vs. RR interval (B) overlaid with a loess smooth line (dashed line, with 95% CI (A)) and a linear regression line (solid line).

### Simulated $\Delta\Delta QTcF$ over a clinically relevant concentration range

- Mean  $\Delta\Delta QTcF$  of 4.33ms (upper limit 90%CI: 7.54) at highest dose level (100 mg, observed  $C_{max}$  = 559.3 ng/mL) [1]
- Mean  $\Delta\Delta QTcF$  > 5ms at 946 ng/mL
- Upper limit of 90%CI > 10ms at 2062ng/mL
  - 3.7-fold safety margin at therapeutic dose of 25 mg QD ( $C_{max}$  = 235.9 ng/mL) [2]

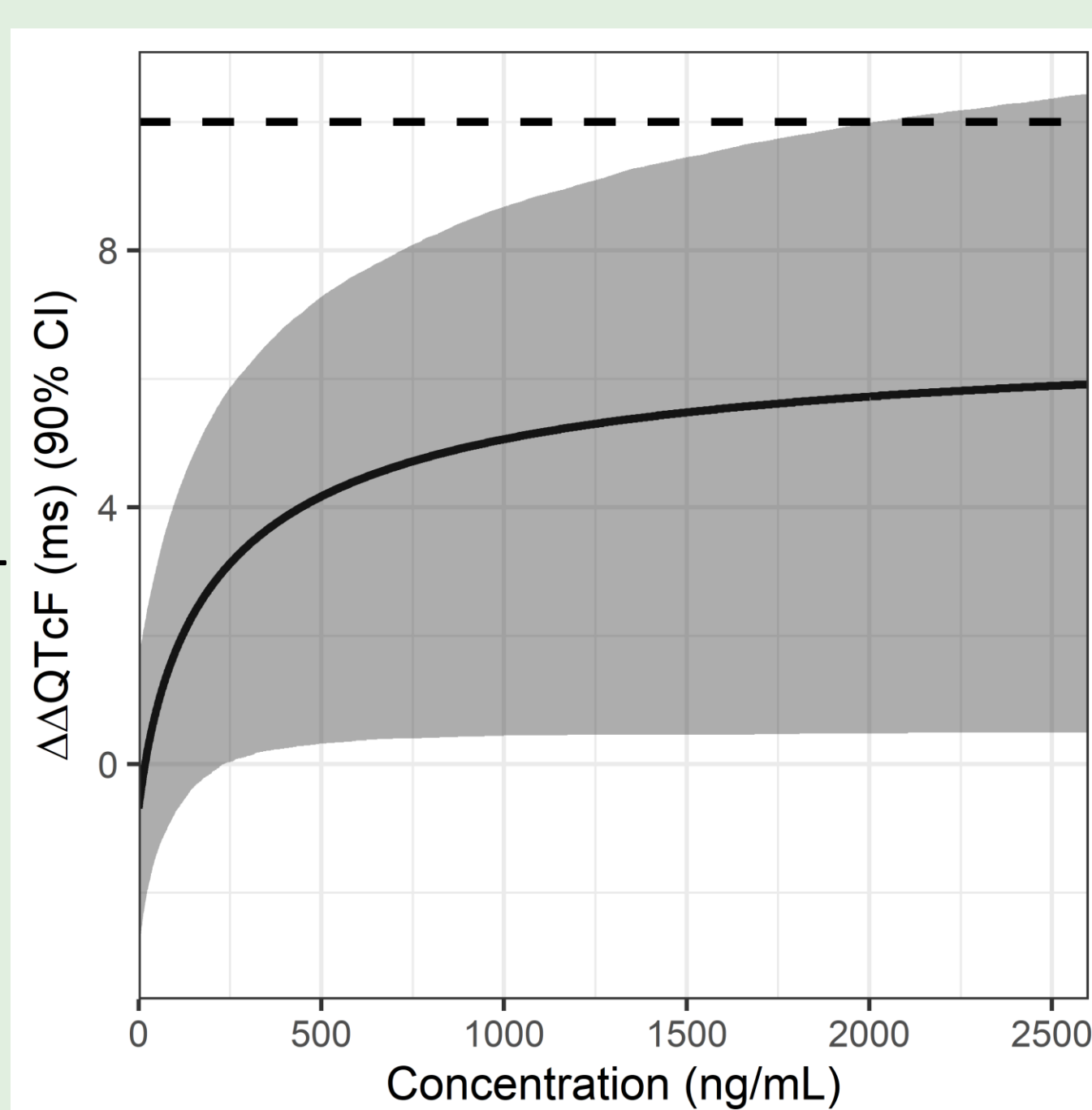


Figure 3. Model predicted  $\Delta\Delta QTcF$  vs darigabat concentration. Mean (solid), 90% confidence interval (grey area) and 10 ms threshold (dashed).

## Conclusion

- The upper limit of the 90%CI of the simulated  $\Delta\Delta QTcF$  reached 10ms at a 3.7-fold higher darigabat concentration than observed at the therapeutic dose of 25 mg QD
- These simulations preclude significant QTc prolongation at clinically relevant darigabat plasma concentrations



## Methods

- Pooled PK and ECG data of 6-100 mg single dose and placebo treatment periods (cross-over) [1]
- Individual mean QTcF values derived from triplicate ECGs and matched to time of PK sampling (pre-dose, 1h, 2h, 4h, 8h, 12h, 24h, 48h post-dose)
  - 639 placebo- and baseline-corrected ( $\Delta\Delta$ ) matched QTcF assessments in 43 subjects
- Application of pre-specified model for conc-QTcF analysis (Eq. 1) [4]
  - Model assumptions (heart rate, hysteresis, linearity)
  - Linear and (sigmoid) Emax relationships
- Calculate mean and 90% confidence interval of simulated  $\Delta\Delta QTcF$  for (therapeutic) concentration range and determine 10 ms threshold concentration

### Adaption of pre-specified model

- Removal of baseline correction (Eq. 1)
- Non-linear Emax relationship (Eq. 2, Table 1)
- Adequate prediction (Figure 2)
  - Especially in higher concentration range (>60 ng/mL)

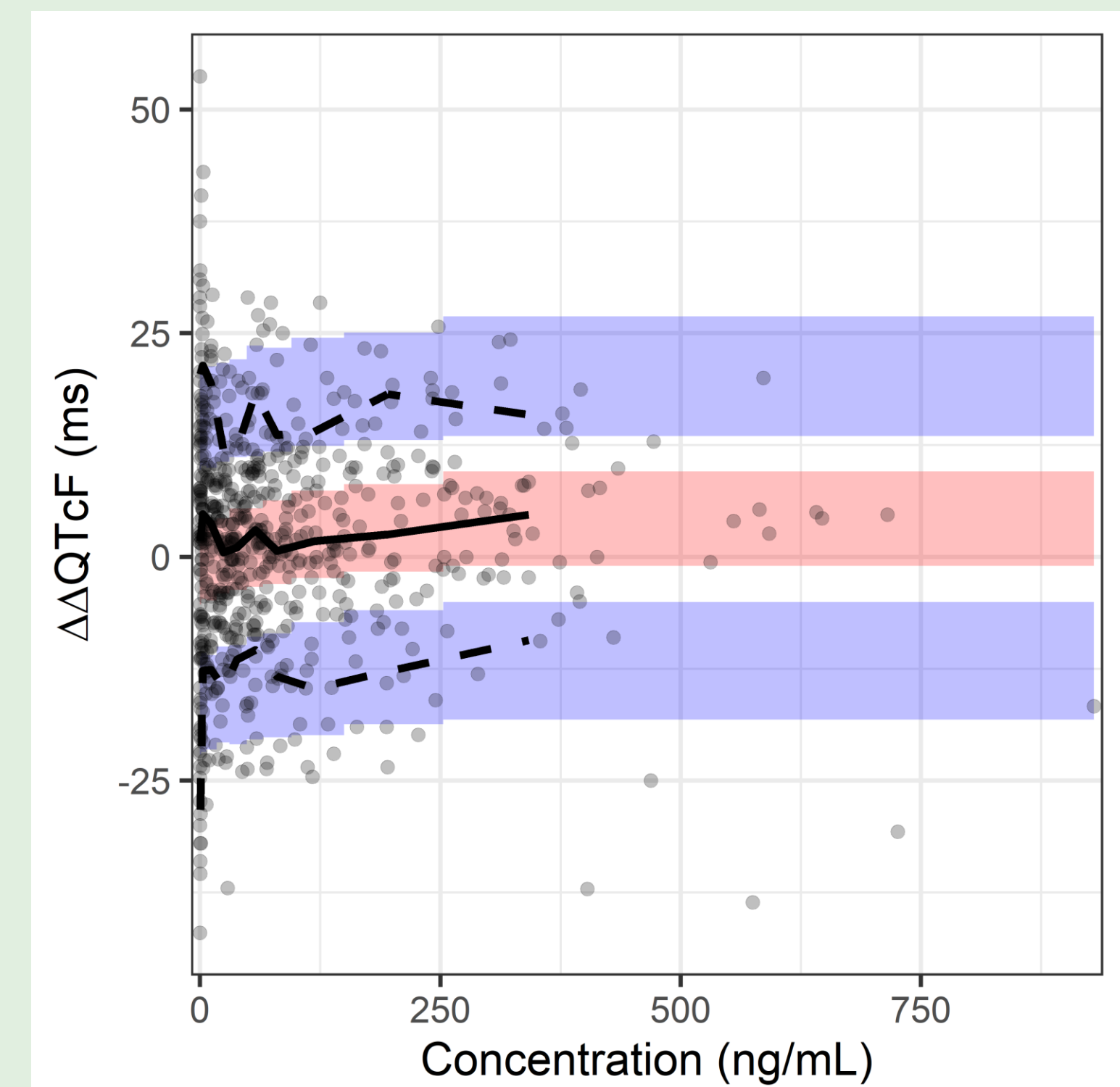


Figure 2. Confidence interval visual predictive check. Median and 80% prediction interval of the data (lines) with simulated 95% confidence interval (colored area).

### Equation 1: pre-specified model

$$\Delta\Delta QTcF = \theta_0 + \theta_1(QTcF_{i,0} - \overline{QTcF}_0) + \theta_2 * C$$

### Equation 2: final conc-QTcF model

$$\Delta\Delta QTcF = \theta_0 + \frac{\theta_2 E_{MAX} * C}{C + \theta_3 EC_{50}}$$

$QTcF_{i,0}$ : individual baseline,  $\overline{QTcF}_0$ : population baseline

Table 1: Parameter estimates for the final conc-QTcF model

Parameter ( $\theta$ )	Estimate	RSE (%)
0. Intercept (ms)	-0.687	207.1
1. Baseline correction	0 FIX	-
2. Emax (ms)	7.43	47.32
3. $e^{\theta EC_{50}}$ ( $EC_{50}$ ng/mL)	5.07 (159)	20.34
<b>IIV and IOV</b>		
$\omega^2$ IIV intercept	49.7	29.66
$\omega^2$ IOV intercept	25.5	29.48
<b>Residual error</b>		
$\sigma^2$ (additive)	86.9	6.08

$EC_{50}$ : concentration at which 50% of the maximum effect is achieved,  $E_{max}$ : maximum effect, IIV: inter-individual variability, IOV: inter-occasion variability

1. Nickolls, S. A. et al. *Br. J. Pharmacol.* **175**, 708–725 (2018).
2. Gurrell, R. et al. *Clin. Pharmacol. Drug Dev.* **10**, 756–764 (2021).
3. Cerevel Therapeutics. <https://investors.cerevel.com/news-releases/news-release-details/cerevel-therapeutics-announces-positive-topline-results> (2022).
4. Garnett, C. J. *Pharmacokinetic Pharmacodyn.* **45**, 383–397 (2018).

