

Handling Hysteresis in Concentration–QTc Analysis: A PK/PD Effect-Compartment Approach Illustrated with Vanoxerine



SimulationsPlus

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INTRODUCTION

- QT analysis may be carried out with **concentration-QTc modeling** based on entry-into-man (SAD and MAD studies) as an alternative to thorough QT (TQT) studies [1].
- The **scientific white paper** (Garnett et al. [2]) provides **technical details** for how to perform conc-QTc modeling, based on a pre-specified linear mixed-effects model
- One of the **assumptions** to be verified before applying the pre-specified model is the **absence of time delay** between the drug concentration and its effect on ΔQTc .
- **When a delay is detected** and cannot be explained by the presence of a metabolite, the white paper suggests using a **PK/PD model with an effect compartment**.
- The derivation of the **$\Delta\Delta QTc$ prediction interval versus concentration** plot from a PK/PD model with delay is not explained in the literature.

OBJECTIVE: Show in practice how to:

- (1) detect a delay
- (2) develop a PK/QTc model
- (3) derive the $\Delta\Delta QTc$ prediction interval versus concentration plot

Case study

Vanoxerine (Preti [3]), a dopamine reuptake inhibitor, is used as an example. Multiple doses of 50 mg or 75 mg of vanoxerine or placebo were administered to 18 cocaine-experienced volunteers over 10 days. **PK and QT data** were collected at 9 matching time points on day 10. Given that a placebo period was available for all individuals, **$\Delta\Delta QTc$ was computed**.

STEP 2: Development of a population PK/QTc model



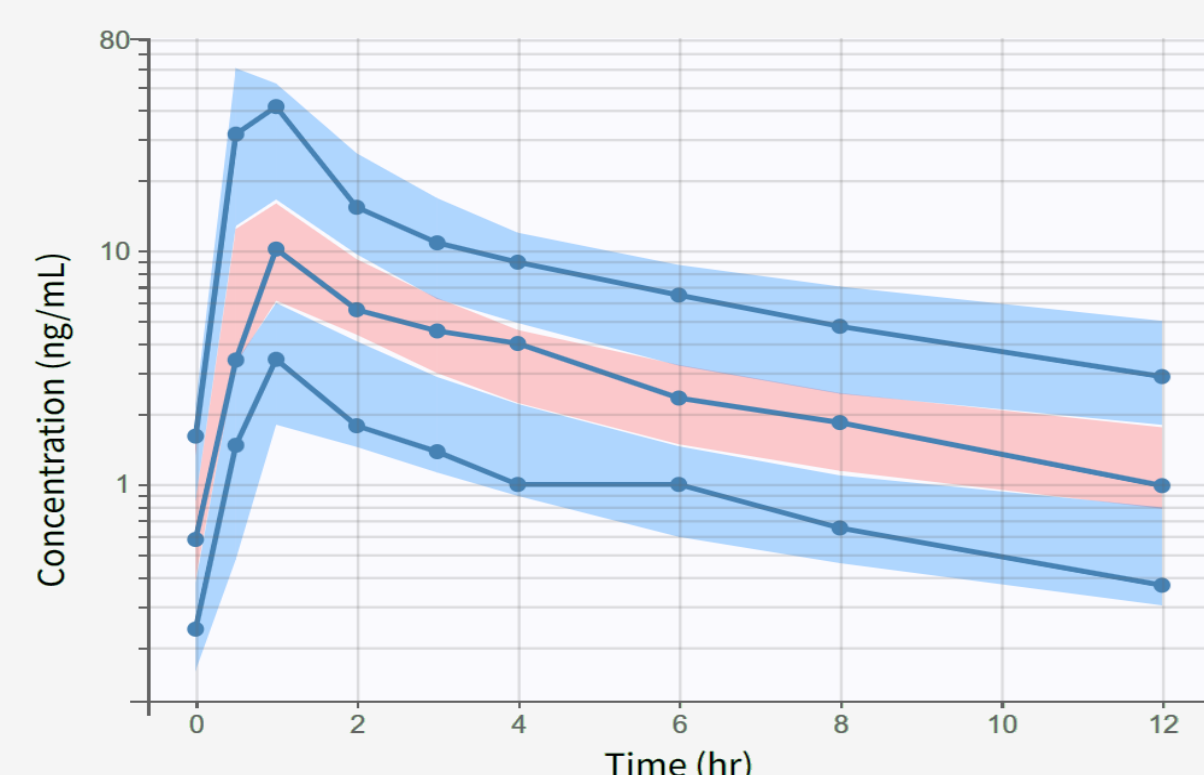
- In case of a delay, the **$\Delta\Delta QTc$ confidence interval cannot be derived using the usual formula** ($\Delta\Delta QTc = \theta_1 + \theta_2 \cdot C$) anymore, where a range of C_c value is used to obtain the corresponding $\Delta\Delta QTc$ values.
- The ΔQTc evolution depends on the **entire past concentration evolution** via the ODE for the effect compartment.

➔ It is necessary to develop a joint population PK/QTc model



PK model:

- A **standard popPK model development** strategy is applied.
- The PK data is well captured by a 2-compartment model with first-order absorption and a lag time.

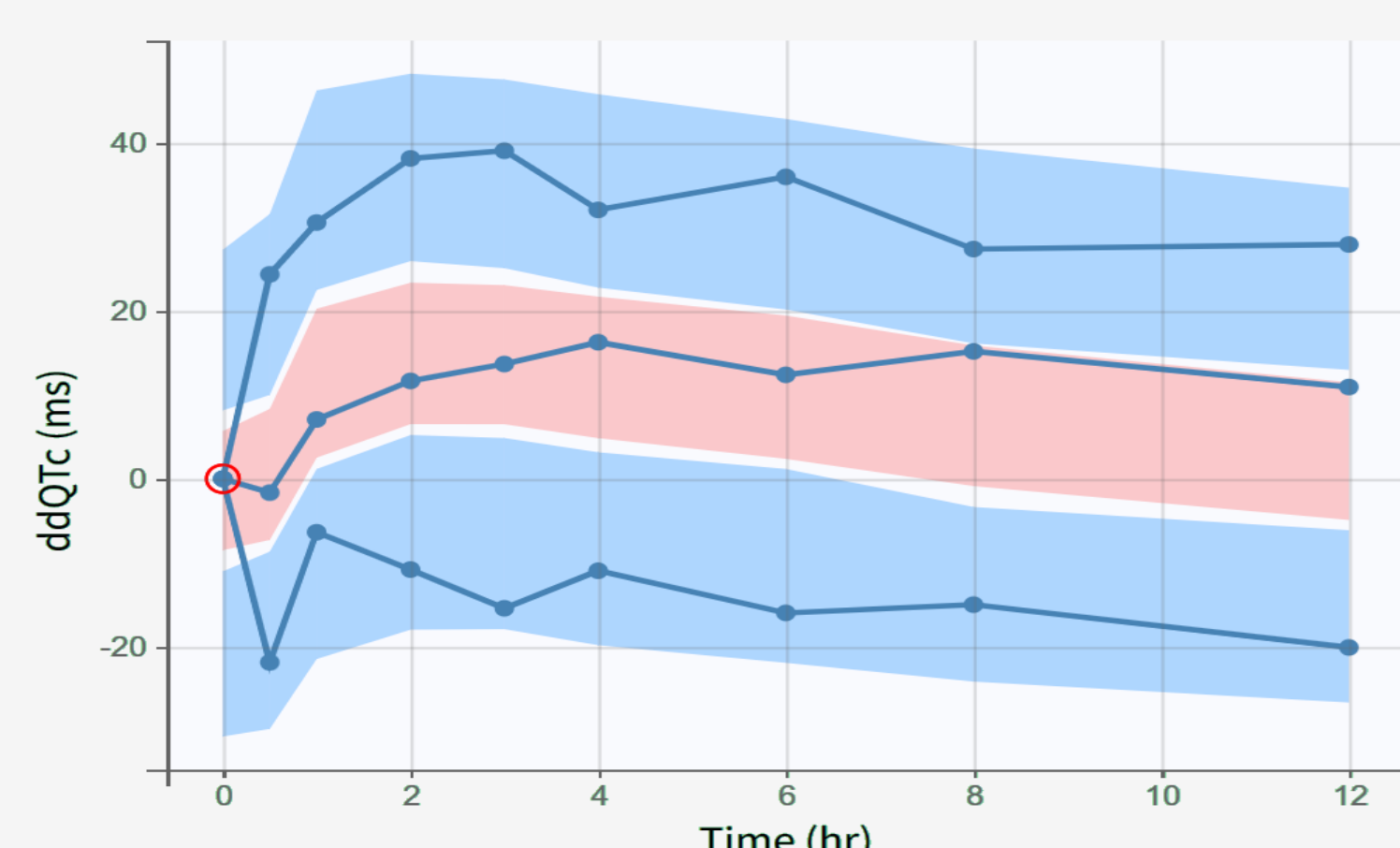


QTc model:

- The white paper pre-specified model is reused, except that the drug concentration is modeled too and it is **the model-predicted concentration which influences $\Delta\Delta QTc$** .
- Several alternative models for the conc- $\Delta\Delta QTc$ relationship are also investigated: **Emax, Hill and log-linear, with or without effect compartment**

Model	-2LL	BICc	$\Delta BICc$ (compared to linear model)
Linear model	1179	1203	
Linear model with delay	1160	1189	-14
Emax model	1165	1195	-8
Emax model with delay	1152	1187	-16

➤ The best model (i.e. lowest BICc) is the **Emax model with delay**



```
[LONGITUDINAL]
input = {Tlag, ka, CL, V1, Q, V2,
         intercept, Emax, EC50, tau}

PK:
{Cc, Ce} = pkmodel(Tlag, ka, V=V1, CL,
                   k12=Q/V1, k21=Q/V2, ke0=1/tau)

EQUATION:
ddQTc = intercept + Emax*Ce/(Ce+EC50)

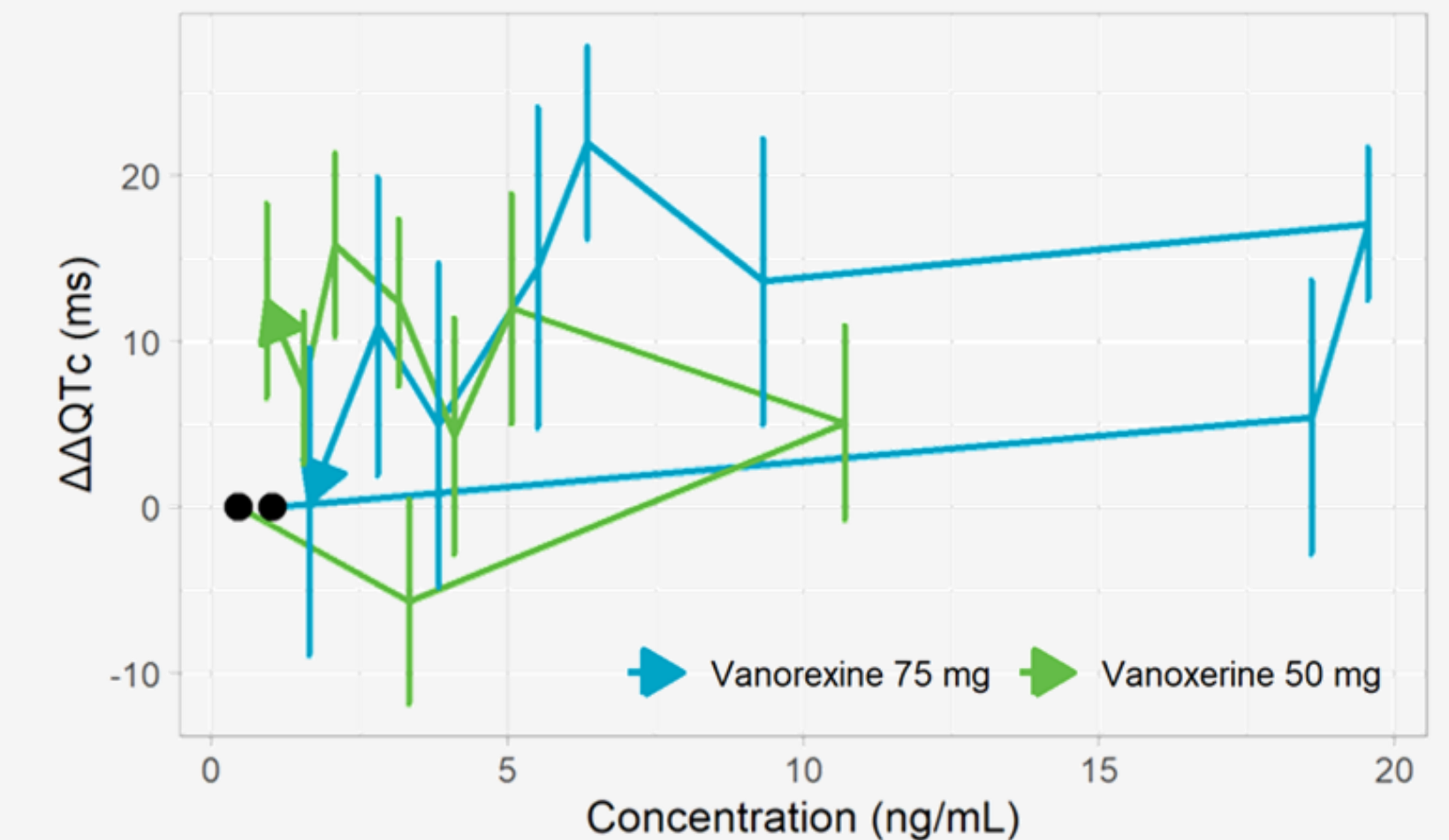
OUTPUT: output = {Cc, ddQTc}
```

STEP 1: Delay detection

The delay detection is done using the **MonolixSuite-based conc-QTc R package** [4].

Visual approach:

- The Garnett et al white paper suggests to detect potential delays between the concentration and its effect on $(\Delta)\Delta QTc$ by plotting the **mean $(\Delta)\Delta QTc$ versus the concentration connected in temporal order by dose**.



- The **counterclockwise loop pattern** suggests the presence of hysteresis, i.e. a delayed effect

Model-based approach:

- The presence of a delay can also be assessed by **comparing the goodness of fit** (via the BICc) of the standard linear model and a **linear model with an effect compartment** to introduce a delay.

Model type	dynamic	BICc	BICc diff. vs direct model	tau0 (hr)
direct	$\Delta\Delta QTc = \Delta\Delta QTc0 + \text{slope} \cdot Cc$	908.9		
indirect	$\frac{dCe}{dt} = (1/\tau0) \cdot (Cc - Ce)$ $\Delta\Delta QTc = \Delta\Delta QTc0 + \text{slope} \cdot Ce$	891.7	-17.2	2.33

BICc: corrected Bayesian information criterion; Cc: drug concentration; Ce: hypothetical concentration in the effect compartment; tau0: time constant to the effect compartment.

- The model with effect compartment is **17 points better** with a delay estimated to be 2.3 hours.

➔ There is evidence of a delay between the drug concentration and its effect on $\Delta\Delta QTc$

STEP 3: $\Delta\Delta QTc$ prediction interval versus concentration plot



- The formula $\Delta\Delta QTc = \theta_1 + \theta_2 \cdot C$ cannot be used anymore because the model input is a dosing regimen with **dose $\Rightarrow C_c \Rightarrow C_e \Rightarrow \Delta\Delta QTc$**
- Because of the delay, the time of maximum concentration and time of maximum $\Delta\Delta QTc$ will be different.
- To create **(conc, $\Delta\Delta QTc$) pairs**, we will consider the **maximum concentration and maximum $\Delta\Delta QTc$** over time for a large range of input dose levels.
- A **typical individual** is simulated (no random effects, BLQTc_centAdj=0) and the **uncertainty of the population parameters** is taken into account by sampling from the FIM.

Setup in Simulx and post-processing:

Sampling from FIM w/o RE:
mlx_TypicalUncertain + reps

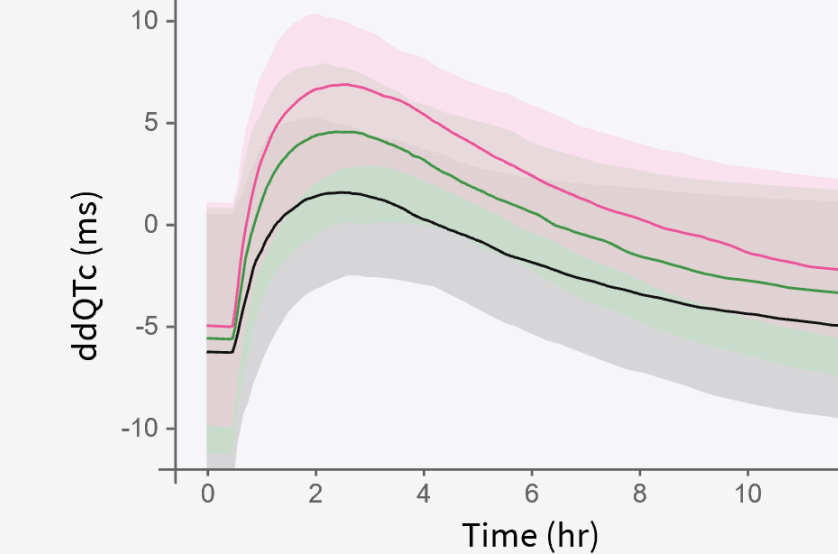
No baseline effect:
BLQTc_centAdj=0

Range of input dose:
Doses from 0 to 100 mg

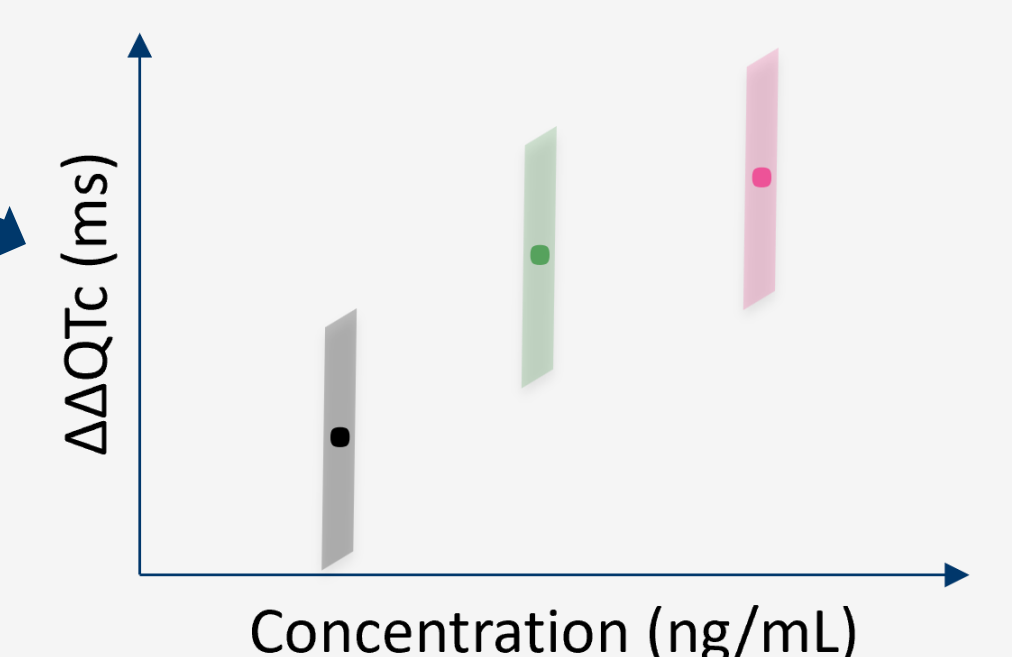
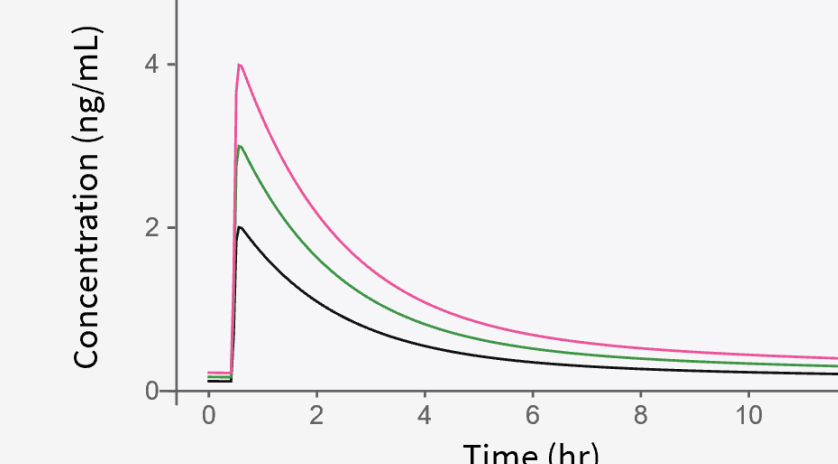
Output on regular grid:
mlx_Cc + mlx_ddQTc

Maximum value:
Outcome "max per id"

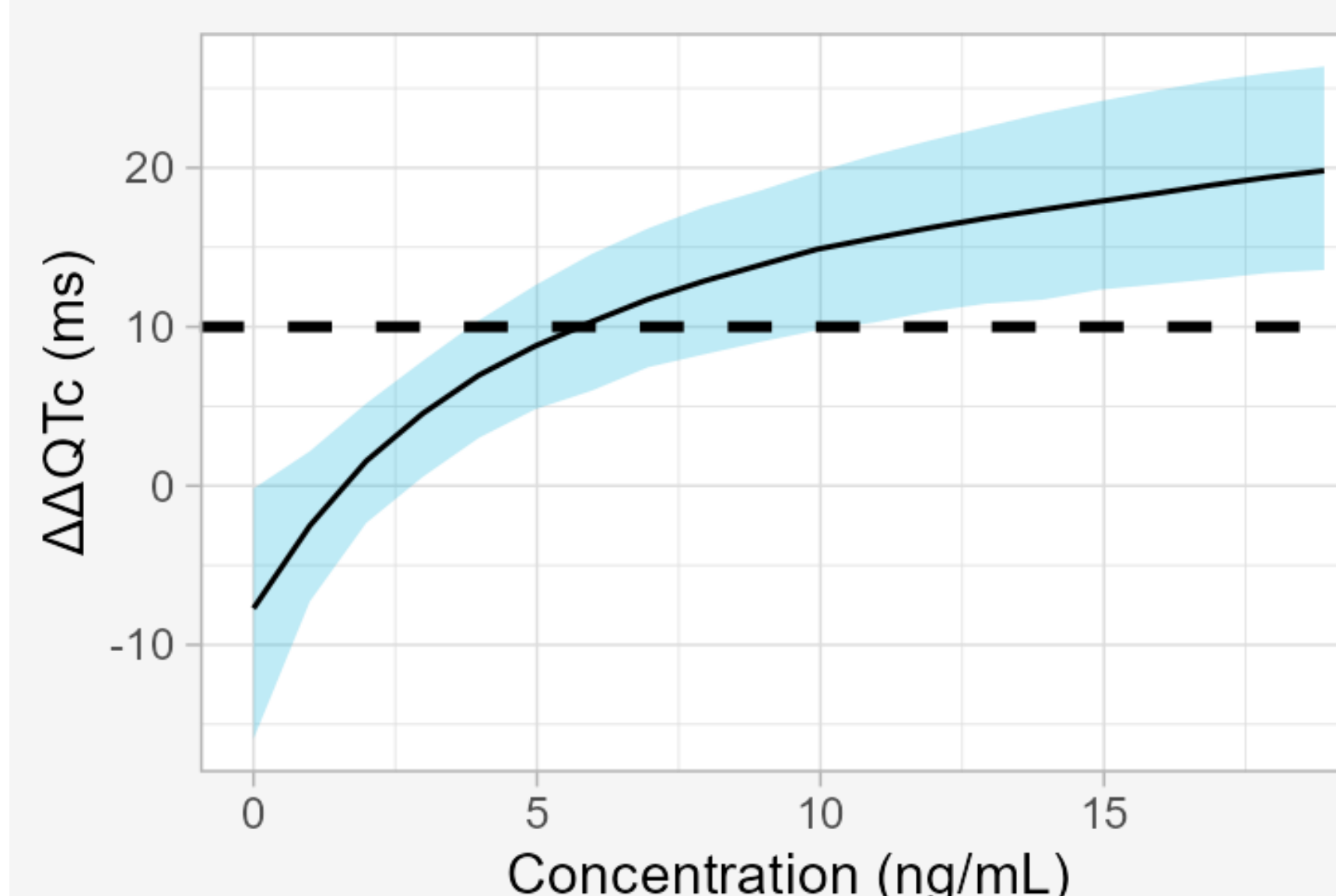
max($\Delta\Delta QTc$) for each dose level and each replicate summarized as 5th, 50th and 95th percentile



max(Cc) for each dose level



Results:



- The **upper bound of the confidence interval** crosses the **10-ms threshold** for a dose of 20 mg, corresponding to an average C_{max} of 4 ng/mL.

- The planned dose of 50 or 75 mg bears a **risk of significant QT interval prolongation**.

➔ Development of Vanoxerine was interrupted because of the QT interval prolongation

REFERENCES

- [1] ICH E14 Guideline: Q&A (2015)
- [2] Garnett et al., *JKPD* (2018)
- [3] Preti A. *Curr Opin Investig Drugs*. (2000)
- [4] Celliere et al., *JKPD* (2025)

Read full case study with downloadable scripts here!



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