Population PK-PD modeling of thorough QT/QTc data allows for mechanistic understanding of observed QTc effects

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Introduction

Thorough QT/QTc trials (TQT) are designed for a yes/no outcome by means of the ICH-E14 statistical analysis. The ICH-E14 method is a very robust tool when the outcome is negative. However, the outcome of a TQT being positive according to ICH-E14 does not necessarily imply a true QTc prolongation effect above the threshold of regulatory concern since the endpoint is known to be biased in case of high variability and for certain study designs.

Since the TQT of drug X was positive (at the supra-therapeutic dose) by means of ICH-E14, the possibility of a Type I error could be investigated and better understanding could be gained by performing a population PK-PD analysis.

The population PK and PK-PD analyses were performed using a non-linear mixed effects modeling approach.

Objectives

- To provide an optimally precise estimate of QTc prolongation associated with drug X;
- To quantify drug and non-drug related effects on QTc prolongation.

Methods

Study overview:

Treatment Arm (parallel)#	N*	Days 1-4	Day 5
Positive Control	N.A.	Placebo orally QD	Moxifloxacin 400 mg orally
Negative Control	44	Placebo orally QD	Placebo orally
Therapeutic dose drug X	44	D mg drug X orally QD	D mg drug X orally
Supra-therapeutic dose drug X	38	5D mg drug X, orally QD	5D mg drug X orally

Note: * number of subjects included in the dataset for the PK-PD model;
study design was valid as shown by the positive control effects on QTc prolongation

Data:

- QTc (with most appropriate correction for heart rate dependence) and PK data from the placebo, active therapeutic and supra-therapeutic treatment arms but not from the active comparator arm was used to build the PK-PD model;
- PK data from 112 subjects (TQT study and previous studies) receiving treatments after doses of 2/3D, D, 2D, 3D, 4D and 5D mg of drug X was used to build a PK model for the simulations with intermediary doses.

PK model:

- two-compartment models with lag time, first order absorption, first order elimination and dose non-linearity were tested.

Baseline model:

- circadian rhythm[2], age, body mass index and race (White / not White) were tested.

Drug effect model (including placebo effect):

- placebo effect was modeled by an additive term to the baseline QTc;
- inter-occasion variability on baseline QTc between baseline (day -1) and after treatment (day 5) was tested;
- linear and exponential direct concentration-response models as well as delayed concentration-response models were tested.

Simulations:

- the effect of drug X on QTc prolongation was also investigated at other doses: 1/3D, 2/3D, 4/3D, 2D, 3D and 4D mg QD by means of simulations;
- simulations (500 samples) from the final PK-PD model were performed to reflect the uncertainty around the mean (upper one-sided 95% CI) for the effect of drug levels on QTc prolongation.

Model selection criteria:

- model selection and identification of covariate effects were based on the Log-Likelihood Criterion, goodness of fit plots and scientific plausibility.
- reliability of the final model was checked with diagnostic plots. Robustness of the models was checked with bootstraps (1000 samples). The adequacy of the models was checked by visual predictive checks (500 samples, stratified by appropriate covariate).

Results

Data:

- individually estimated QT correction was chosen as primary endpoint.

PK model:

- the structural PK model was a two-compartmental model with lag time, first order absorption and first order elimination;
- no demographic effects were found on the PK of X.
- the dose non-linearity between the PK of the therapeutic and supra-therapeutic doses was captured by allowing the peripheral volume (Vp) and intercompartmental clearance (Q) for high doses (doses ≥ 3D) to be different than the ones for low doses (doses < 3D): Vp.highDose ≈ 3*Vp.lowDose and Q.highDose ≈ 5*Q.lowDose;
- the model adequately described PK time course over a large range of doses (1/3D – 5D) as shown by a VPC (not included).

Baseline model:

- linear model with an intercept parameter, QTc0, and between-subject variability;
- circadian rhythm with 2 oscillators with a rhythm of 6 and 12 hours;
- sex and age were significant on baseline QTc and both covariates were incorporated;
- the model adequately described QTc time course as shown by a VPC (not included).

Drug and placebo effect:

- placebo effect was incorporated;
- a time delay (about 2h) was observed between Cmax and peak dQTc;
- drug effect was incorporated as a linear term depending on drug levels in a hypothetical effect compartment;

- the effect compartment was modeled as: $\frac{dCe}{dt} = K * (Cp - Ce)$
- the final concentration-effect model was:

$QTc0_i = QTc0 + \eta_{1i} + \eta_{IOVi}$

$CIRC_i = A_{1i} \cos [\, 2\pi (t - \phi_{1i}) / 12] + A_{2i} \cos [\, 2\pi (t - \phi_{2i}) / 6]$

$QTc_{ij} = (QTc0_i + Peff + Sex + Age) * (1 + CIRC_i) + SL*Ce_{ij} + \varepsilon_{ij}$

Table 1. Parameters of the final PK-PD model

Parameter (unit)	Symbol	Estimate	90% CI Bootstrap
QTc baseline value (ms)	QTc0	409	(406, 412)
Between-subject variability (ms)	η1	12.6	
Inter-occasion variability (ms)	IOV	3.8	
Amplitude 12 h (ms)	A1	0.00386	(0.0028, 0.0049)
Acrophase 12 h (hours)	ϕ1	9.25	(8.92, 9.56)
Amplitude 6 h (ms)	A2	0.00504	(0.0045, 0.0058)
Acrophase 6 h (hours)	ϕ2	5.68	(5.51, 5.83)
SEX ~ QTc baseline (ms)	Sex	-18.5*	(-22.2, -14.6)
AGE ~ QTc baseline (ms)	Age	0.411	(0.2, 0.63)
Placebo effect (ms)	Shift	-4.44	(-5.33, -3.55)
Rate constant from effect compartment (h^{-1})	K	0.337	(0.275, 0.431)
Slope of drug effect (ms)	SL	0.00177	(0.00144, 0.00211)
Residual variability (ms)	ε	5.1	

QTc baseline in a typical 30 year old woman was 409 ms

Men had a 18.5 ms lower QTc baseline than women

QTc baseline increased with 0.411 ms per year

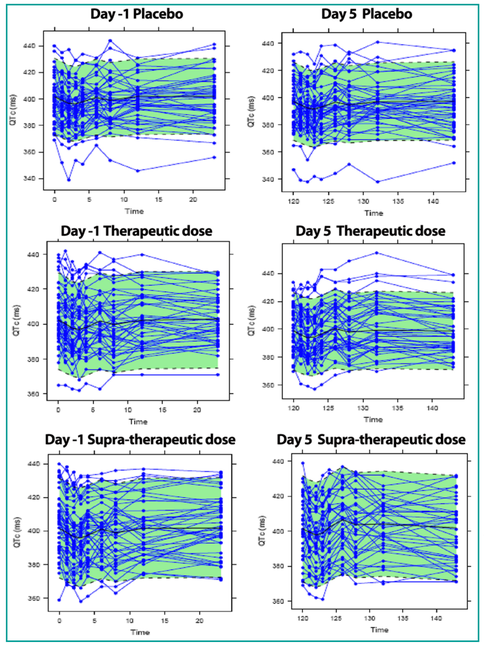
QTc baseline was 4.44 ms lower after treatment then at baseline

The mean drug effect on QTc is linearly dependent on concentrations of X in the hypothetical effect compartment, increasing with 0.00177 ms/(ng/mL)

Note: RSE is Relative standard error as estimated by NONMEM
90% CI Bootstrap is P5 –P95 of 1000 bootstrap results.

- a bootstrap with 1000 samples stratified on treatment group and day showed the robustness of the model;
- a VPC (Figure 1) with 90% coverage based on 500 samples stratified by dose and day showed that the model had good agreement with the observations.

Figure 1. VPC (90% coverage) of the final PK-PD model by dose.



Note: blue markers and lines are observed QTc; Shaded green area goes between the 5-th and 95-th percentiles of the simulated predictions; Black line is the mean of the simulated predictions.

Simulations:

- the uncertainty in the predictions of QTc effect was addressed by drawing parameter samples from across the variance-covariance matrix of the model parameters correlated to the drug effect (SL, Peff and K).

Table 3. Predicted placebo-corrected dQTc at (plasma) mean Cmax of the therapeutic and supra-therapeutic doses from this trial as well as simulated dosing regimens.

Regimen	Mean Cmax ng/mL	Mean Cemax ng/mL	PK-PD model on QTc		ICH-E14 results	
			dQTc# (ms)	Upper 95%CI#	dQTc^ (ms)	Upper 95%CI^
1/3D mg QD	1060	543	1.0	1.1		
2/3D mg QD	1950	1085	1.9	2.3		
D mg QD*	3000	1788	3.2	3.8	3.6	6.5
4/3D mg QD	3460	2178	3.9	4.6		
2D mg QD	4860	3260	**5.8**	6.9		
3D mg QD	5180	3293	**5.8**	6.9		
4D mg QD	6330	4376	**7.7**	9.2		
5D mg QD**	7470	5285	**9.4**	**11.2**	**9.5**	**12.5**

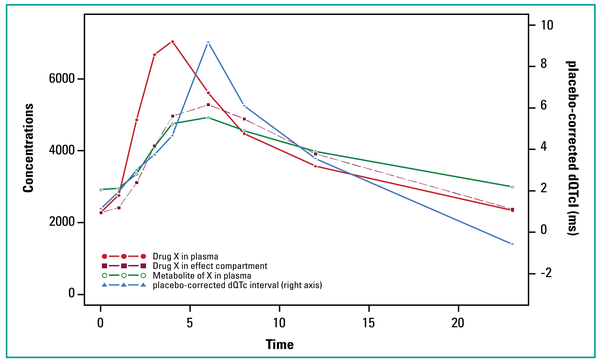
Note: * therapeutic and ** supra-therapeutic doses of this trial;
Cmax: peak plasma concentrations of drug X;
Cemax: drug concentrations in the effect compartment of the final PK-PD model;
bold values denote mean dQTc values exceeding 5 ms or upper 95% CI values exceeding 10 ms.
predicted placebo-corrected dQTc calculated as Slope*Cemax
^ largest time-matched placebo-corrected dQTc (at 6 hours). This was the single time point where the upper 95% CI exceeded 10 ms.

Discussion

- despite the negative hERg tests performed on drug X and a metabolite (at therapeutic dose) the PK-PD model confirmed an effect on QTc prolongation slightly above the threshold of regulatory concern;
- the PK-PD model for QTc predicts a mean placebo-corrected dQTc above 5 ms for doses above 4/3D mg X;
- the PK-PD model for QTc predicts the one-sided upper 95% CI of the mean placebo-corrected dQTc above 10 ms for doses above 4D mg X.

In general drugs exert their effect (if any) on QT/QTc prolongation immediately. The delayed effect on QTc prolongation detected graphically and confirmed by the model suggests that it might not be drug X causing the QTc prolongation, but possibly a derivative that takes some time to be formed after administration of the parent. Metabolite concentrations next to drug X and QTc prolongation showed a good alignment between the metabolite peak and peak QTc prolongation. Further, metabolite vs. time profile aligned well with drug X concentrations in the hypothetical effect compartment, providing support for the use of the effect compartment model to characterize the effects of drug X on QTc prolongation, see Figure 2.

Figure 2. Drug X, metabolite and dQTc vs. time in the supra-therapeutic dose group



Note: red line is drug X plasma concentrations (mean observed Cp per time point) on the left axis; dark red dashed line is drug X concentrations in the effect compartment (mean predicted Ce per time point); green solid line is metabolite plasma concentrations (mean observed Cmet per time point); blue line is dQTc vs. time (mean observed dQTc per time point) on the right axis.

Conclusion

A population PK-PD model was successfully fitted to the data of a TQT trial. Metabolite vs. time profile aligned well with drug X concentrations in the hypothetical effect compartment and peak QTc prolongation, allowing for mechanistic understanding of observed QTc effects. The TQT was positive and the PK-PD model could confirm a QTc prolongation effect slightly above the threshold of regulatory concern.

References

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2. V Piotrovsky et al, Pharmacokinetic-Pharmacodynamic Modeling in the Data Analysis and Interpretation of Drug-induced QT/QTc Prolongation, The AAPS Journal 2005; 7 (3) Article 63

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