Introduction

Thorough QT/QTc trials (TQT) are designed for a yes/no outcome by means of the ICH-E14 statistical analysis. The ICH-E14 is a very strict tool when the outcome is negative. However, the outcome of a TQT being positive according to ICH-E14 does not necessarily lead to 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 (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:

Objectives

• PK model: the structural PK model was a two-compartmental model with lag time, first order absorption and first order elimination and doses non-linearity were tested.
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Model selection criteria:

- Model selection and identification of covariate effects were based on the Lassègue-Cox criterion, goodness of fit plots and scientific plausibility
- Reliability of the final model was checked with diagnostic plots. Robustness of the model was checked with bootstrap (1000 samples). The adequacy of the models was checked by visual predictive checks (500 samples, stratified by appropriate covariates).

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);
- Acrophase 12 h (hours);
- 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, QTCi, 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 QT time courses 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 QTc;
- Placebo effect was incorporated;
- The effect of drug X on QTc prolongation, see Figure 2.

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).

Conclusions

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, 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


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

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