

Use of a drug-drug interaction study with itraconazole to quantify the effects of an NME on QT interval duration



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1 – Introduction

During clinical development of a new pharmaceutical agent, it is critical to examine its effect on ECG parameters, due to the ability of some non-antiarrhythmic drugs to delay cardiac repolarization. Cardiac repolarization can increase the risk of “torsade de pointes” (TdP) which can lead to sudden cardiac death. QT interval prolongation is a surrogate marker of TdP.

Objective
Assess the QT interval prolonging effect at supra-therapeutic exposure of a new molecular entity (NME) using a DDI study.

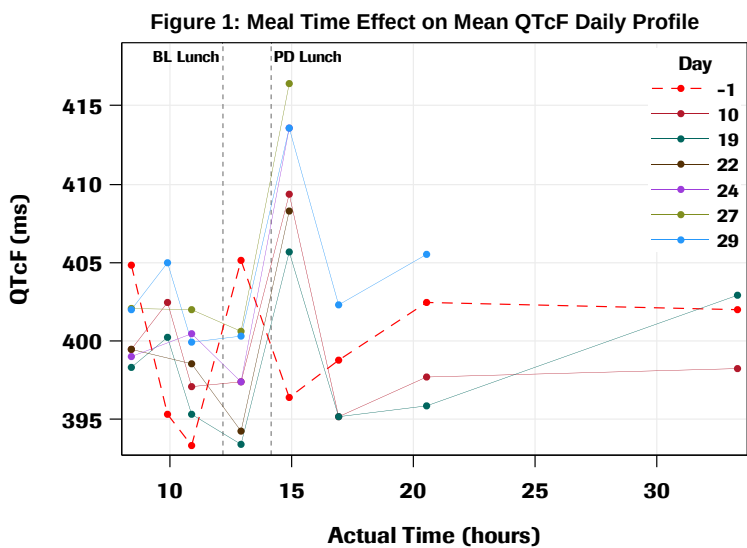
2 – Materials & Methods

Data:
A clinical DDI study was conducted to evaluate the pharmacokinetics and QT prolonging effect of the NME (mainly metabolized by CYP3A4) with and without concomitant administration of the potent CYP3A inhibitor itraconazole. The study was a single center, non-randomized, open-label, three-treatment, fixed sequence crossover as shown in the below table

Table 1: Treatment Schedule							
Period 1		Period 2		Period 3			
Day 1	→ Day 10	Day 15	→ Day 19	Day 20	→ Day 29		
NME b.i.d		200 mg Itraconazole b.i.d		NME b.i.d + 200 mg Itraconazole b.i.d			

Subjects received dose D1 (n = 4) or D2 (n = 8) of the NME . ECGs were collected at baseline and serially paired with PK samples on Day 10 (NME alone) and on Day 29 (NME with itraconazole) and at select time points on Days 19, 22, 24, and 27.

There was a mismatch of meal times between Day -1 and dosing days with breakfast and lunch given one to two hours earlier on Day -1. Therefore postprandial increases occur at different times as shown in Figure 1 below and time-matched changes from baseline do not properly account for the effect of meal time.



Models:
An observed concentration-QT (C-QT) approach that integrates models of the different QT component was used to characterize the relationship between QT interval and plasma concentrations of both the NME & Itraconazole.
As shown in equations (1) and (2) below, the model has the following features:

- Individualized correction of heart rate as described by the parameter α
- Circadian variations of QT model using oscillatory functions: different periods were tested
- Effects of meal time on circadian parameters were quantified
- Different types of C-QT models were tested with and without interaction between the NME and itraconazole. The final drug model is linear for the NME and itraconazole

$$QT_{Baseline} = \frac{MES}{RR^\alpha} \cdot \left(1 + Amp_6 \cdot \cos\left(2\pi \frac{time - Acr_6}{6}\right) + Amp_{12} \cdot \cos\left(2\pi \frac{time - Acr_{12}}{12}\right) \right) \quad (1)$$
$$QT = QT_{Baseline} + NMEEffect + ItraconazoleEffect \quad (2)$$

MES: is the average value around which the QT oscillates, **RR**, the time between to consecutives RR peaks-during the ECG. **Amp6** and **Amp12** are the amplitudes. **Acr6** and **Acr12** are the acrophases.

Population data analysis
The data were modeled using a nonlinear mixed effects modeling approach in NONMEM (version 7.2 Icon Development Solutions, Ellicott City, MD) for the parameters estimation and SAS 9.4 was used for graphical analyses of the results. Residual variability was modeled with an additive error model. Model development and qualification were guided by the objective function (OFV), the goodness of fit plots (GOF) and the precision of parameter estimates.

4 – Results

The estimated population parameters, the precision of their estimation (RSE) and the coefficient of variation (CV) are given in Table 2 for the final model. The VPC and PPC results show that the final PKPD model describes well the data and can be used for simulations.

Table 2: Population PK parameters for the final model

Parameters	Unit	Estimate	RSE (%)
Fixed Effect Parameters			
θ_1 Mes	ms	399.3	1
θ_2 α	-	0.299	9
θ_3 Amp6	-	0.0161	9
θ_4 Amp12 Baseline	-	0.0077	35
θ_5 Amp12 Postdose	-	0.00896	8.9
θ_6 Acr6 Baseline	h	1.142	8
θ_7 Acr6 Postdose	h	3.23	2
θ_8 Acr12 Baseline	h	-4.938	11
θ_9 Acr12 Postdose	h	2.40	8
θ_{10} Slope NME	ms.mL/ng	0.000455	25
θ_{11} Slope Itraconazole	ms.mL/ng	-0.00365	40
Random Effect Parameters			
ω_1^2 BSV on Mes	% CV	32	18
ω_2^2 BSV on α	% CV	2.6	28
ω_3^2 BSV on Amp12 Postdose	% CV	43.9	20
ω_{11}^2 BSV on Slope Itraconazole	% CV	0.4	26
θ_{12} Additive residual error	ms	4.7	5

Figure 2: Simulated NME effect on QT prolongation

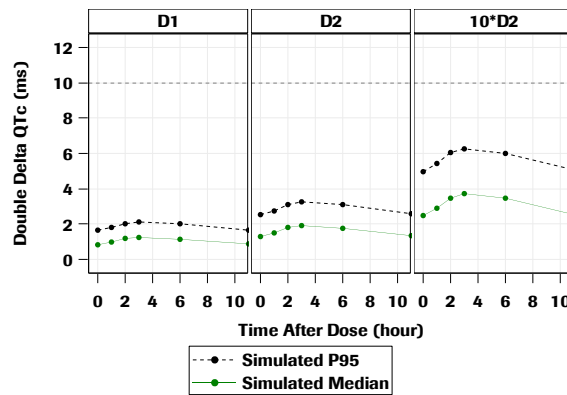


Figure 2 shows the simulated P95 and median of the placebo-corrected changes from baseline of QTc ($\Delta\Delta QTc$) for different doses of the NME at steady.

It appears that the effect of NME on QT prolongation is unlikely to be of clinical concerns even at dose 10-fold higher than the dose used in clinic (D2).

Figure 3: Simulated NME effect on QT prolongation with 33% of Clearance

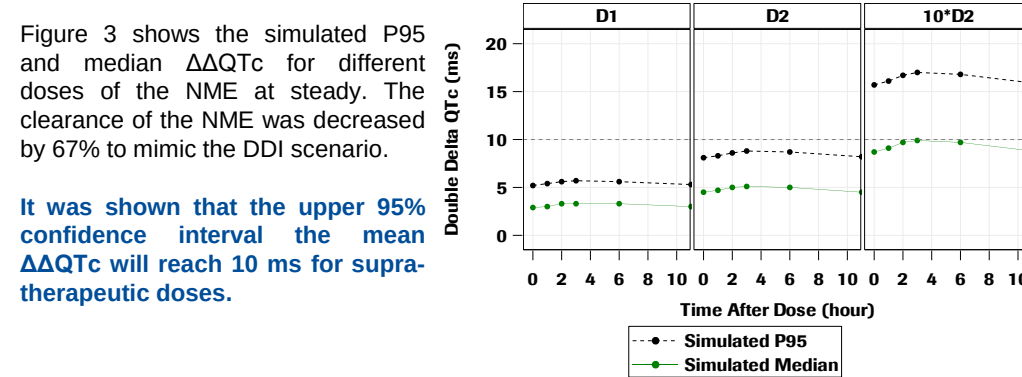


Figure 3 shows the simulated P95 and median $\Delta\Delta QTc$ for different doses of the NME at steady. The clearance of the NME was decreased by 67% to mimic the DDI scenario.

It was shown that the upper 95% confidence interval the mean $\Delta\Delta QTc$ will reach 10 ms for supra-therapeutic doses.

Figure 4: NME effect with uncertainty

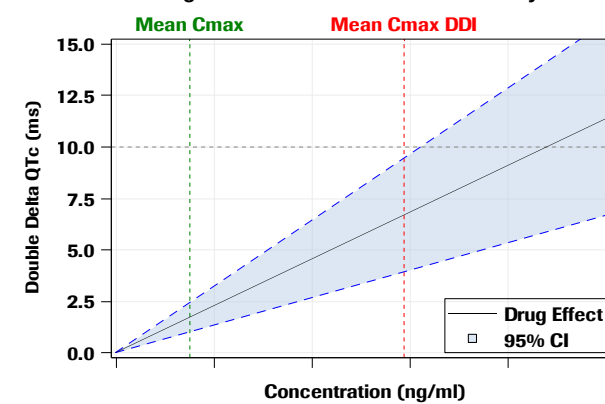


Figure 4 illustrates the worse case scenario: the uncertainty in the slope of the NME effect is taken into account.

These simulations show that with a potent CYP3A4 inhibitor Cmax of the DDI might be close to 10 ms threshold.

5 – Discussion

- An exposure-response model that adequately evaluates the drug effects of the NME on cardiac repolarization was developed.
- Meal time effect and treatment effect are actually confounding factors in this study as both of them were changed from baseline to post-dose. Therefore it was assumed that drug is not affecting the amplitude of the circadian in order to estimate the effect of meal time on the amplitude.
- The model although based on a small sample size appropriately differentiated the drug-induced QT prolongation from other factors altering QT Interval duration.
- It was shown by simulations that the magnitude of the NME effect on QT prolongation is unlikely to be of clinical concern even at high exposures.

6 – References

- [1] ICH E14 Guidance. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. European Medicines Agency, November 2005
- [2] Vladimir Piotrovsky. Pharmacokinetic-Pharmacodynamic Modeling in the Data Analysis and Interpretation of Drug-induced QT/QTc Prolongation., October 2005