Implementation of the C-QTc study using MonolixSuite applications

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INTRODUCTION

International Council for Harmonisation (ICH) E14 guidance agreed to use a model-based study of **concentration-QT data as a primary analysis** in the proarrhythmic risk assessment

Modelling guidelines: pre-specified LME model presented in "Scientific white paper on concentration-QTc modelling" by Ch. Garnett et al. (J. Pharmacokinet. Phar. 2017)

- Check the model assumption via exploratory plots
- Develop the relationship between a drug concentration and the change from baseline of the heart rate corrected QT interval corrected by placebo ($\Delta\Delta$QTc)
- Compute the mean $\Delta\Delta$QTc at concentration of interest and 90% double sided confidence interval
- Assess if the QTc prolongation exceeds the 10ms regulatory threshold

Decision criteria

Upper bound of the 90% 2-sided CI of mean $\Delta\Delta QTc$ should be <10ms at the highest relevant exposure

Goals:

1. Implement in Monolix the pre-specified LME model.
2. Perform the C-QT risk assessment according to the FDA recommendations.
3. Develop a joint PK- $\Delta\Delta$QTc model in Monolix and perform the risk assessment for new dosing regimens in Simux GUI.

Case study:

Dofetilide: class III antiarrhythmic agent known to prolongate the QT interval

Design:

- Crossover study (drug-placebo) with 7 days washout
- 22 adults who received a single oral dose of 500µg

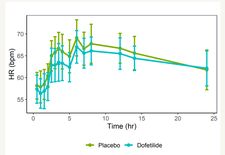
Dataset:

- Time matched observations at 16 pre-defined time points
  - Defetilide concentration
  - 3 optimal 10-sec 12-lead ECG recordings
- Pre-dose baseline
- Covariates: population centered baseline, weight, age, sex

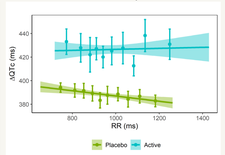
2. STANDARD C-QTc ANALYSIS

Exploratory plots

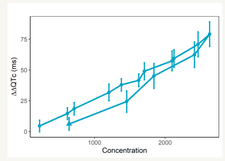
H1: No drug effect on the heart rate HR (HR vs time)



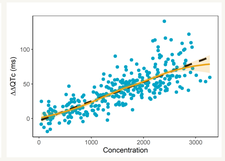
H2: QTc independent of HR (QTc-RR quantile plot, LME line and 95% C.I.)



H3: Direct effect between the mean $\Delta\Delta QTc$ (with the 90% C.I.) and concentration



H4: Linearity and heterogenity between the $\Delta\Delta QTc$ and concentration



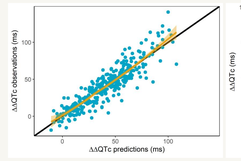
Model results and diagnosis

Population parameter estimates

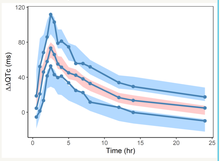
	VALUE	STOCH. APPROX. S.E.	STOCH. APPROX. R.S.E.(%)
Fixed Effects			
intercept_pop	-3.63	1.36	37.5
beta_intercept_Blcent	-0.89	0.12	13.7
slope_pop	28.47	1.42	5.01
Standard Deviation of the Random Effects			
omega_slope	5.56	0.9	16.1
Error Model Parameters			
a	12.01	0.48	4.02

Population parameters estimated by the SAEM algorithm using Monolix

Obs. Vs pred. with the Loess smooth line and 95% C.I.

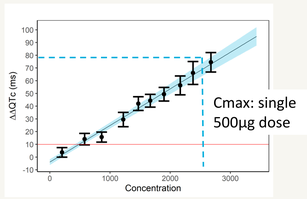


VPC (solid lines: empirical percentiles; areas: 10th, 50th and 90th prediction intervals)



Decision criteria

Confidence interval is simulated by sampling $intercept_{pop}$ and $slope_{pop}$ from the normal distribution with sd. based on se. estimated by Monolix.



$\Delta\Delta QTc$ pred. w.r.t drug conc. with the mean and s.e. of the $\Delta\Delta QTc$ obs. for the active groups represented in 10 bins and 95% C.I.

1. ΔΔQTc MODEL IMPLEMENTATION IN MONOLIX

Pre-specified Linear mixed effects model:

i – individual
j – treatment (drug/placebo)
k - time

$$\Delta QTc_{ijk} = \theta_0 + \eta_{0,i} + \theta_1 TRT_j + (\theta_2 + \eta_{2,i})C_{ijk} + \theta_3\, TIME_k + \theta_4\left(QTc_{i,j,k=0} - \overline{QT}c_{j,k=0}\right)$$

$\Delta\Delta QTc_{ik} = (\Delta QTc_{ijk})_{drug} - (\Delta QTc_{ijk})_{placebo}$
Drug: j = 1, $TRT_1 = 1$
Placebo: j = 0, $TRT_0 = 0, C_{i,0,k} = 0$

$$\Delta\Delta QTc_{ik} = \underbrace{\theta_1 + \theta_4\left(\left(QTc_{i,0} - \overline{QT}c_0\right)_{j=1} - \left(QTc_{i,0} - \overline{QT}c_0\right)_{j=0}\right)}_{\text{intercept}} + \underbrace{(\theta_2 + \eta_{2,i})C_{ijk}}_{\text{slope}}$$

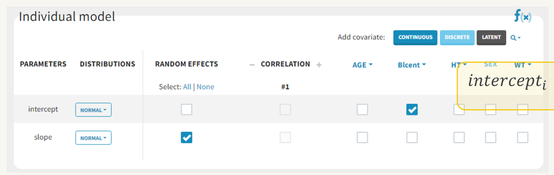
continuous covariate (placebo corrected population centred baseline)

Cc regressor

Structural model in the model file

```
[LONGITUDINAL]
input = {Cc, intercept, slope}
Cc = {use = regressor}
EQUATION:
ddQTcF = intercept + slope*Cc
OUTPUT:
output = ddQTc
```

Statistical model in the Monolix interface



$$intercept_i = \underset{\theta_1}{intercept_{pop}} + \underset{\theta_4}{\beta_{intercept}} \cdot BLcent_i$$

$$slope_i = \underset{\theta_2}{slope_{pop}} + \underset{\eta_{2,i}}{\eta_{S,i}}$$

Estimated mean $\Delta\Delta QTc$

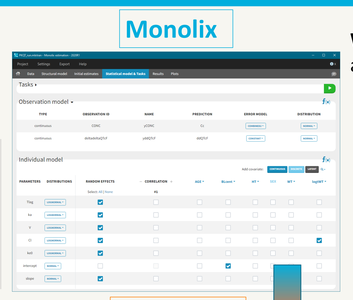
$$\Delta\Delta QTc(C) = intercept_{pop} + slope_{pop} \cdot C$$

3. ADVANCED PK-QTc MODEL & SIMULATIONS

- PK: 1cmt model with time delay, linear absorption and linear elimination
- ΔΔQTc: pre-defined linear mixed effect model with effect compartment

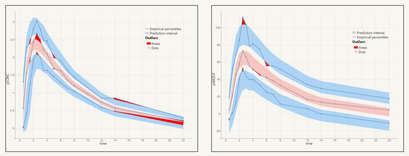
```
[LONGITUDINAL]
input = {Tlag, ka, V, Cl, ke0,
intercept, slope}
EQUATION:
{Cc, Ce} = pkmodel(Tlag, ka, ke0, V, Cl)
ddQTcF = intercept + slope * Ce
OUTPUT:
output = {Cc, ddQTcF}
```

Monolix



Wald test: β parameters are significative

VPC:

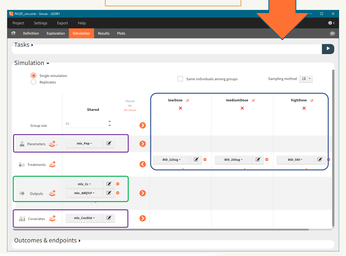


Model comparison:

	(ka, Cl, V)	+Tlag	+effect cmt
BICc	3029	2686 (-343)	2598 (-112)
$slope_{pop}$	32.08 (r.s.e. 8%)	30.08 (r.s.e. 4.8%)	29.4 (r.s.e. 5%)

Simulx GUI

- 3 groups with different treatments: 125, 250 and 500 µm BID
- Individual parameters simulated using population parameters estimated by Monolix and covariates from the original dataset
- Output: model predictions for the concentration and ΔΔQTc



Prediction distribution (left) for the ΔΔQTc with the 10ms threshold and the number of individuals (right) with max(ΔΔQTc)>10ms