SIMULATING CARDIAC CONSEQUENCES OF THE GENETIC VARIABILITY AT THE METABOLISM LEVEL WITH USE OF MIDDLE-OUT APPROACH AND FLECAINIDE AS AN EXAMPLE COMPOUND

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Background

Recent activities lead towards limiting TQT studies and increasing role of phase I clinical trial results and in vitro data connected by the mathematical models [1,2]. The aim of this study was to assess whether modeling and simulation (M&S) can be used to predict cardiac consequences of an example drug with use of middle-out approach by utilization early clinical trial data (PK) and in vitro drug triggered cardiac ionic currents disruption, and therefore support novel (M&S based) approach [3].

Methods

Flecainide was chosen as a model drug due to diverse in nature cardiac effects. Additionally flecainide is metabolized mainly by CYP2D6 therefore is susceptible to the genetic variation at the level of the enzyme activity.

Simcyp platform V13.1 (Figure 1) with minimal PBPK and first order absorption models was used to simulate individual plasma concentrations based on the pre-clinical and clinical (CLpo) ADME data for the population of extensive (EM) and poor (PM) metabolizers (Table 1). Cardiac Safety Simulator V1.0 (Figure 2) was used to simulate cardiac electrophysiology and simulation was performed at the level of the one dimensional string of cardiac ventricular cells.

Table 1. *ADME parameters utilized for Simcyp simulations.*

Parameter	EM 50 mg	PM 50 mg	EM 100 mg	PM 100 mg
Clpo (CV)	34.92 (40)	23.58 (19)	28.62 (33)	22.38 (23)
Mol Weight (g/mol)	414.34			
log P	3.78			
Compound Type	Monoprotic Base			
pKa 1	9.30			
B/P	0.89			
fu	0.61			
Vss (L/kg)	4.90 (8.0)			
PSA(Å²)	59.60			
HBD	2.00			

Individual exposure data was further utilized as CSS input together with *in vitro* ionic channels inhibition data (IC50 values in µM): I_{Kr} = 3.91, I_{Na} = 0.9. Simulations were set to mimic single clinical trial: n=12 individuals, including 7 extensive metabolizers (EM) and 5 poor metabolizers (PM) for 2D6, mean age 25.8 ± 4.5 years (23-37), 50 and 100 mg tablets, multiple dosing (BID – 9am/9pm).

Plasma concentration and effect measured 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after final dose (5th day). Predicted free plasma concentrations for the above defined time points were utilized in all cases during simulations. PD endpoints included drug triggered modification of the electrocardiographic parameters – QRS, QT/QTcF, JT/JTcF.

Figure 1. *Simcyp platform (V13.1) utilized during the study.*

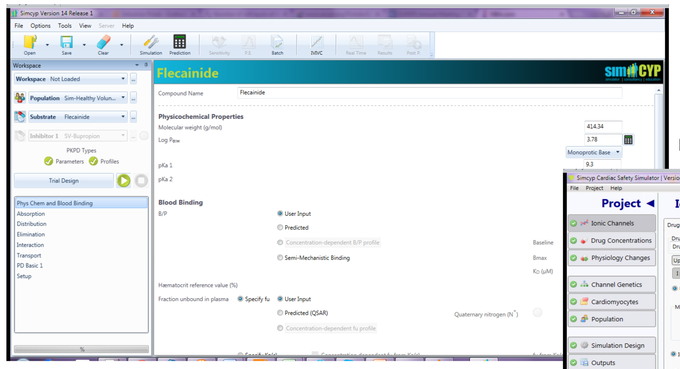
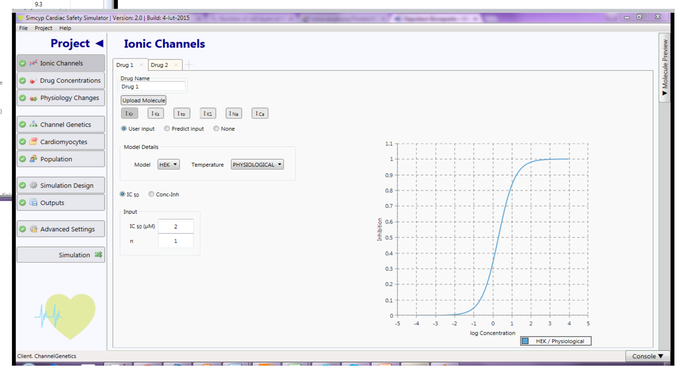


Figure 2. *CSS V1.0 utilized during the study.*



Results

Figure 3 and Figure 4 present PK and PD simulation results as compared with the observed values for four simulation .

Figure 3. *Pharmacokinetic simulation results for 4 populations.*

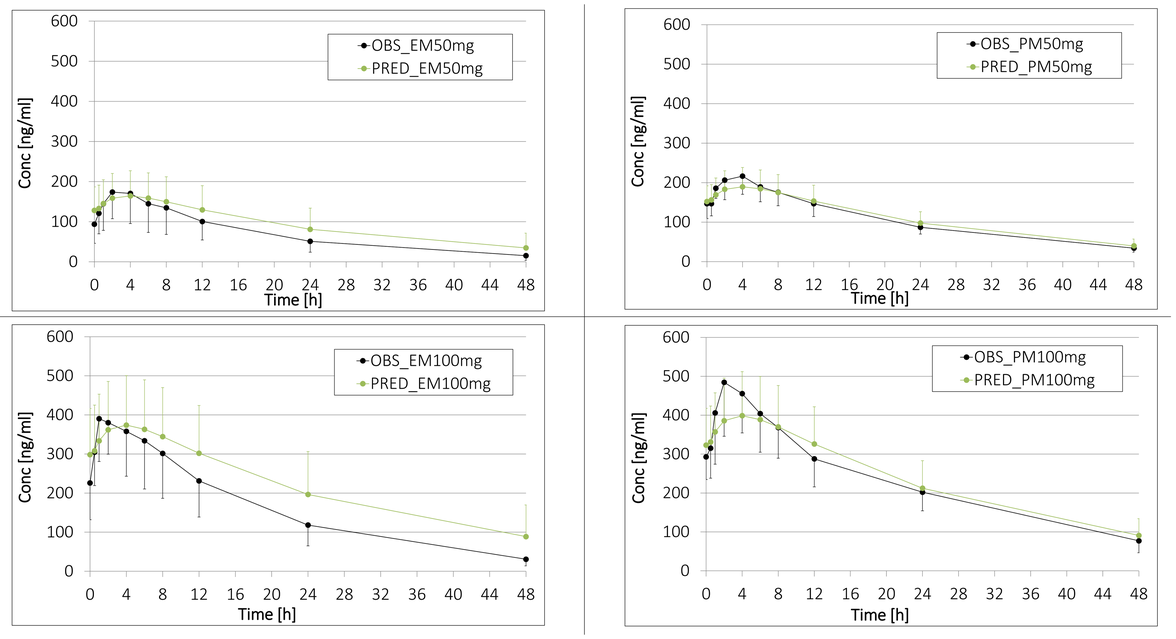
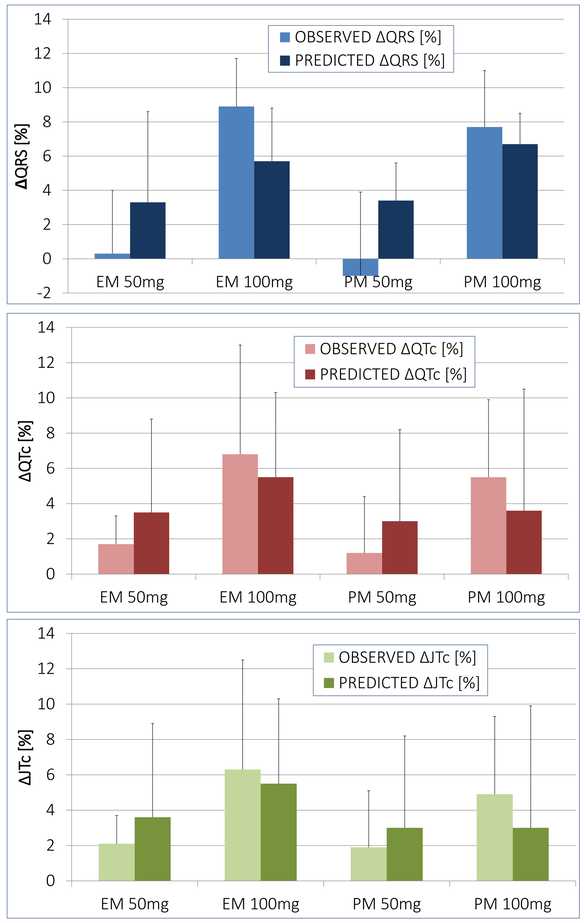


Figure 4. *Pharmacodynamic simulation results for 4 populations.*



Discussion & Conclusions

The results support predictive abilities of the *in silico* simulations and their potential utilization for the cardiac safety assessment as it was recently presented in other published studies [3]. Combination of early clinical data utilized via the empirical pharmacokinetic model and in vitro data describing drug triggered ionic currents inhibition allowed for precise prediction of the cardiac consequences at the population level. In all cases differences between observed and predicted values were statistically not significant. Importantly dispersion around average values for all simulated endpoints (QRS, QTc and JTc) mimicked those observed clinically. Potential limitation of the study lies in lack of potentially active metabolites in simulations.

References

1) Sager PT, et al. AmHeartJ 2014;0:1-9; 2) Darpo B. et al. ClinPharmTher 2014 DOI: 10.1002/cpt.60; 3) Glinka 2014 ComputBiolMet: 7:20-26