**Introduction**
Cardiotoxicity assessment is a compulsory element of the drug development process required by the drug agencies including FDA and EMA [1,2]. The risk of fatal ventricular arrhythmia triggered by drugs is the rationale for such requirements. Over the last two decades prolongation of QT interval has been responsible for the withdrawal of several drugs from the market and the expensive black box labeling restrictions. Although there are a number of mechanisms by which drugs may lead to QT prolongation, the inhibition of the potassium channels encoded by the hERG gene has been a cause in many cases and interaction with hERG channel has become a major pharmacological safety concern. The potential pharmacological and toxicological effects – except the idiosyncratic reactions – are dose dependent. IVIVE incorporated into PBPK provides the opportunity of simulating variability of ADME in large populations, ‘prior’ to conduct of clinical trials. Combination of this approach with any information on concentration-effect relationship may assist with identifying the likelihood of observing pharmacological or toxicological effects, an essential step in study design.

**Objectives**
The main objective of the current project was to assess potential cardiotoxic risk, including inter-individual variability, by combining the in silico mechanistic cardiomyocyte model and PBPK models. Clozapine as a non-cardiology drug has been associated with potential harmful cardiac side effects [9]. This drug was used as an example.

**Methods**
Simcyp V10.1 IVIVE/PK platform was used for the prediction of clozapine concentrations in plasma and heart tissue after oral dosing. Simulation settings were as follows:
- single 25 mg oral dose
- first order absorption (ka = 2.22 [h⁻¹])
- full PBPK disposition - heart tissue-to-plasma partition coefficient was calculated to be 6.16 [3]

North European Caucasus - 6 individuals as presented in the tables below, to assess inter-individual variability in PK
- plasma and heart tissue concentrations as the operational concentrations for the pharmacodynamic effects.

**Results**
Maximum plasma and heart tissue concentrations, different for every individual, were chosen as the operational concentration. Information regarding the clozapine influence on the ion channels was derived from the literature and is presented below (Table 1) [7,8].

**Discussion**
Results presented above need to be interpreted further to gain some conclusions which could be relevant for the drug development specialists. One of the few possible ways is to calculate and analyze pseudo-ECG rather than AP only. Obtained results were compared with clinical observations for clozapine. Predicted increase in APD₉₀ (~7%) doesn’t suggest substantial increase in QT length although some influence might be observed. As it was recently published by De Ponti there are some clinical evidence suggesting the influence about clozapine influence on QT but the prolongation potential is low [9]. Among other factors influencing drugs QT prolongation potential genetic element plays a significant role. There is an ongoing project which aims at incorporating genetic variability to the virtual population and assessing quantitatively its impact.

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**References**