CERTARA

Cardiac Safety Simulator

A simulation-based platform to assess QT interval prolongation risk

The Challenge

Drug-induced QT interval prolongation is considered a surrogate marker for a potentially fatal cardiac arrhythmia (Torsades de Pointes). Systemically bioavailable small molecule drugs must therefore be assessed during clinical development in a Thorough QT study or via Concentration-QT Modeling. QT prolongation in such studies can lead to drug discontinuation or a slower and more costly development phase culminating in QT prolongation risk on the label. A pre-clinical assessment of QT prolongation risk is therefore essential.

The Solution: Cardiac Safety Simulator (CSS)

- Support early cardiac liability predictions through cardiac ion channel QSAR models.
- Simulate the effect of cardiac ion channel block of up to 7 compounds (co-medications; metabolites) on ventricular myocyte action potential duration and QT interval.
- Incorporate human population variability.
- Reduce reliance on animal and clinical studies.

Assessing pro-arrhythmia risk throughout the development cycle

Discovery

QSAR model for IKr, IKs, INa and ICaL

CSS provides quantitative structure activity relationship (QSAR) models for predicting IKr, IKs, INa and ICaL block based on automatically calculated physical chemistry data (when *in vitro* data are not available). All QSAR models were developed with artificial neural networks in conjunction with novel enhanced QSAR methodology. The latter combines molecular descriptors of the compound of interest with parameters relating to the *in vitro* assessment of a specific ion channel's inhibition.

Preclinical

Electrophysiology

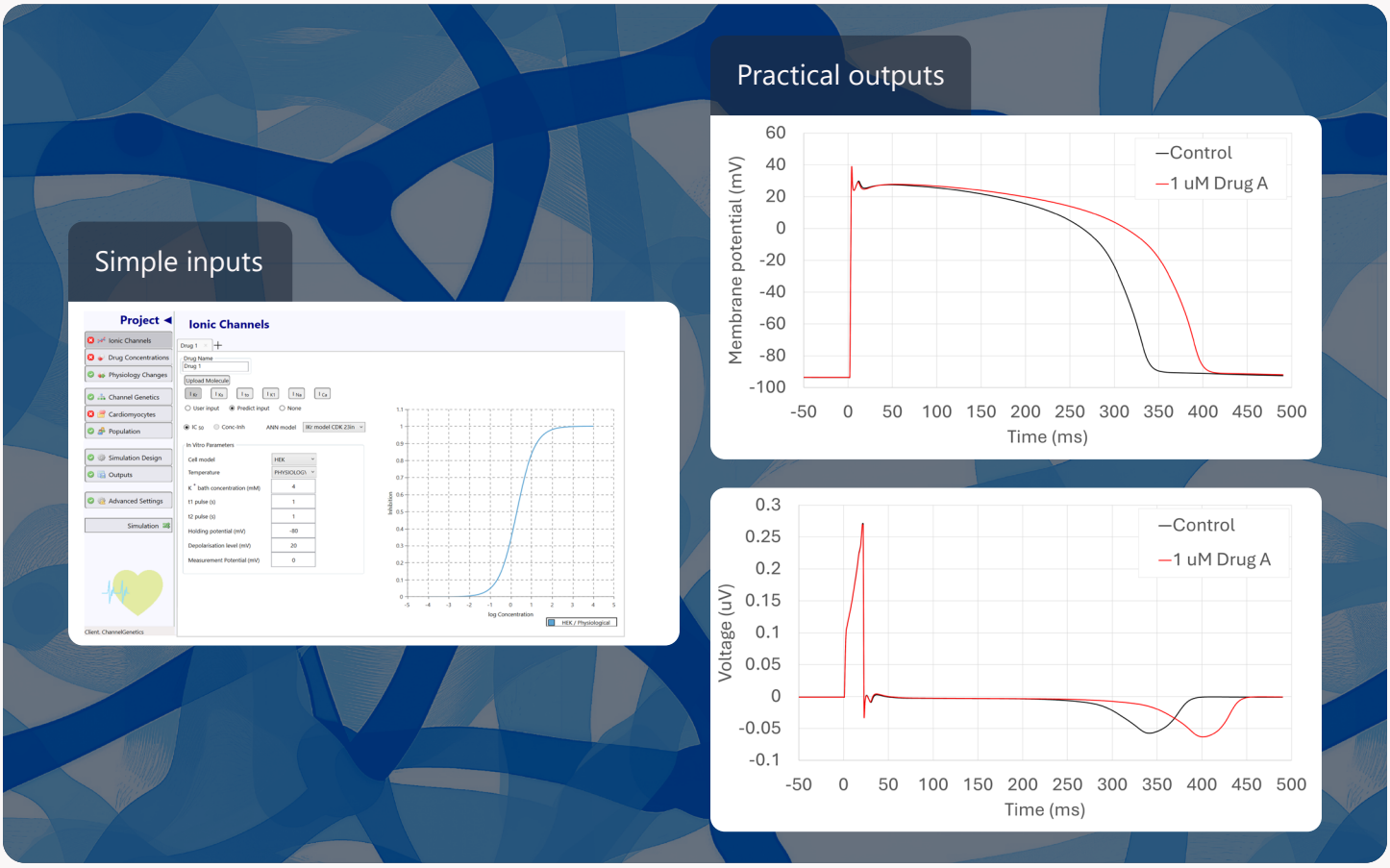
CSS uses models of human heart ventricular cells to mathematically describe cardiac cell electrophysiology as an action potential of membrane dynamics. This can integrate population variability from sex, age or circadian dependent variability including heart rate, ion concentrations (K^+, Na^+, Ca^+), maximum current density and more to interrogate cardiotoxicity within varying population features.

Clinical

ECG

CSS includes a one-dimensional (1D) fibre model that incorporates transmural heterogeneities in ionic currents between endocardial, mid-myocardial and epicardial cells. Results from the one-dimensional fibre model are used to generate a virtual ECG for automatic calculation of its derivatives, including QRS, QT, J-T_{peak}, and T_{peak}-T_{end}.

The CSS interface:



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Why use CSS?

- Multi-scale detection of QT prolongation risk from ion channel inhibition to ECG.
- Integration with Simcyp® Simulator software to link population-based physiologically based pharmacokinetics (PBPK) for comprehensive PK-linked drug assessment.
- Excel®-based simulation outputs for easy visualization and analysis.
- Support clinical trial design including dosing schedule and volunteer population.

Relevant publications

Glinka A, Polak S.
QTc modification after risperidone administration – insight into the echanism of action with use of the modeling and simulation at the population level approach. *Toxicol Mech Methods.* 2015; 25: 279-86.

Wisniowska B, Mendyk A, Szlęk K, Kołaczkowski M, Polak S.
Enhanced QSAR models for drug-triggered inhibition of the main cardiac ion currents. *Appl Toxicol.* 2015; 35: 1030-9.

Mishra H, Polak S, Jamei M, Rostami-Hodjegan A.
Interaction Between Domperidone and Ketoconazole: Toward Prediction of Consequent QTc Prolongation Using Purely In Vitro Information. *CPT Pharmacometrics Syst Pharmacol.*, 2014; 3, e130.

Fijorek K, et al.
Model of the distribution of diastolic left ventricular posterior wall thickness in healthy adults and its impact on the behavior of a string of virtual cardiomyocytes. *Journal of Cardiovascular Translational Research,* 2014; 7(5): 507-517.

Glinka A, Polak S.
The Effects of Six Antipsychotic Agents on QTc – an attempt to mimic clinical trial through simulation including variability in the population. *Computers in Biology and Medicine*, 2014; 7:20-26.

Wisniowska B, Mendyk A, Fijorek K, Polak S.
Computer-based prediction of the drug proarrhythmic effect – problems, issues, known and suspected challenges. *Europace,* 2014;16:724-735.

Polak S, Wisniowska B, Fijorek K, Glinka A, Mendyk A.
In vitro-in vivo extrapolation of drug-induced proarrhythmia predictions at the population level. *Drug Discovery Today,* 2014; 19:275-281.

Fijorek K, Püsküllüoglu M, Polak S.
Circadian models of serum potassium, sodium and calcium concentrations in healthy individuals, and their application to cardiac electrophysiology simulations at individual level. *Computational and Mathematical Methods in Medicine*, 2013; Article ID 429037, 1-8, 2013; doi:10.1155/2013/429037.

Wiśniowska B, Holbrook M, Pollard C, Polak S.
Utilization of mechanistic modelling and simulation to analyse fenspiride proarrhythmic potency - Role of physiological and other non-drug related parameters. *J Clin Pharm Ther*, 2022;47: 2152-2161.

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,400 biopharmaceutical companies, academic institutions and regulatory agencies across 66 countries.

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