Assessing the role of local heart tissue concentration in bottom-up mechanistic prediction of QT prolongation by moxifloxacin using PBPK-QSTS modeling

N Patel, M Jamei, B Wisniowska, S Polak
Objectives

1. Bottom up prediction of QT prolongation and TdP risk for moxifloxacin (MOXI)

2. Estimate the relevant exposure in bio-phase

3. Translate *in vitro* hERG IC$_{50}$ to clinical ECG level with QSTS model

4. To study the impact of uncertainty/lab-to-lab variability in *in vitro* hERG IC$_{50}$ value on model outcome

5. To verify the model performance to simulate the torsade de pointes (TdP) event
PBPK Model including Mechanistic Absorption model
PBPK-QSTS Approach for QT prolongation/TdP risk assessment

A

PBPK Model

Exposure (PK)

(multiple) moieties

Electromechanical (EM) window

cell contractility

- AP prolongation
- AP shape analysis
- EADs

hERG

in silico (QSAR)

in vitro (measured)

other ion currents

in silico (QSAR)

in vitro (measured)

CONTRACTILITY MODEL

HUMAN HEART LEFT VENTRICULAR CELL MODEL

virtual population

action potential (APD90)

pseudoECG (QTc)

- QT prolongation
- iCEB
- J-Tpeak, Tpeak-Tend

demography

physiology

genetics

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What is reference point?

Variability in reported QT prolongation after 400mg Moxifloxacin oral dose

Impact on in vitro hERG IC50 on model outcomes

Uncertainty/variability in in vitro input could affect interpretation

Strong need to standardise or select a common reference \textit{in vitro} protocol to move forward
Predicted QT prolongation with various bio-phase inputs

Unbound Plasma

Total Plasma

Unbound Heart Tissue

Total Heart Tissue

Sim Individual – Obs Mean – Sim Mean – Sim Female Mean – Sim Male Mean
• ten Tusscher 2006 model shows unbound heart tissue exposure as bio-relevant
• O’hara-Rudy 2011 model shows total plasma exposure as bio-relevant
**TdP is multi-factorial event**

Simulated pseudoECG traces after therapeutic (red thick line), supra-therapeutic (double green continuous line) exposure of MOXI to

(A) healthy physiology

AND

(B) with tachycardia and hypokalaemia

FAERS database mining indicates almost all TdP cases where MOXI was involved were multi-factorial and TdP occurred when combined with other risk factors e.g. hypokalemia and abnormal heart rate.
Towards Bridging Translational Gap in Cardiotoxicity Prediction: an Application of Progressive Cardiac Risk Assessment Strategy in TdP Risk Assessment of Moxifloxacin

Nikunj Kumar Patel, Oliver Hatley, Alexander Berg, Klaus Romero, Barbara Wisniowska, Debra Hanna, David Hermann, and Sebastian Polak

Early Discovery Screening
- Virtual chemical structure based screening possible
- No accurate exposure/PK needed
- Quick single cell level simulations

Cardiac Risk Algorithm
- Prioritise compounds
- Low/Moderate/High Risk of TdP
- FIH dose guidance
- Guidance on in vivo animal studies

hERG/other channel
in silico (QSAR)

hERG/other channel
in vitro (measured)

CSS Platform
HUMAN HEART LEFT VENTRICULAR CELL MODEL

Drug(s) + (active Metabolite) Exposure

Late Stage Clinical TdP Risk Assessment
- Incorporate accurate PK information including active metabolites
- Assess metabolic or cardiac (PD) level DDI
- Assess cardiotoxicity in varied clinical circumstances such as disease or genetic polymorphisms, environmental factors

Increasing clinical knowledge of the drug, more model verification and confidence in prediction

Quantitative approach for cardiac risk assessment and interpretation in tuberculosis drug development

Sebastian Polak, Klaus Romero, Alexander Berg, Nikunj Kumar Patel, Masoud Jamei, David Hermann, Debra Hanna

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THANK YOU