**Introduction**

QT interval prolongation is considered as a biomarker of torsade de pointe (TdP) in cardiac safety assessment in drug development. While specific QT/QTc studies are usually performed in healthy volunteers, allowing an accurate estimation of such noisy data as QT interval length, those approaches are not feasible in the specific context of oncology, where patients only can receive the drug. A model-based strategy, including population approach may help the description of PKPD relationship while taking into account all sources of variability but the clinical constraints of phase I/II studies in oncology limit electrocardiogram (ECG) schedules.

**Objective**

Our aim is to propose a cardiac safety assessment method, based on both optimal sampling design and population PKPD modelling. The ultimate goal is to estimate the power of detection of any potential effect of an anticancer drug on QT interval length.

**Methods**

**Baseline poly-cosine QT model:**

- Built on a thorough QT/QTc study data (62 + 87 healthy volunteers):
  - Exponential inter-individual variability (IIV) on every parameter.
  - Additive residual error model.

\[
Q(t) = Q_{0}(t) + \sum_{i=1}^{n} Q_{i} \cdot \cos \left( \frac{t - T_{i}}{2 \pi / 2} \right)
\]

**Drug effect is assumed linear on Mesor:**

\[
Q_{0}(t) = Q_{0}^\text{ref} + \gamma \cdot (t - T)
\]

**PK model:**

The chosen PK model was a 3-compartment model, with first order absorption and elimination. Inter-Individual Variability (IIV) on every parameter except inter-compartment constants and 2nd peripherical volume.

**Power of detection of a drug effect:**

The model described above was then used in order to evaluate an ECG measurement schedule. The Fisher Information Matrix (FIM) relative to a known design was computed with PopDes 3.0, thus giving the precision of estimation of the model parameters. The result distribution of drug effect parameter was then used to assess the power (1 - RSE %) of the design.

**Results**

**Baseline poly-cosine QT model:**

Parameter values and relative standard error (RSE)

<table>
<thead>
<tr>
<th></th>
<th>QT4a (ms)</th>
<th>QT1a (hour)</th>
<th>QT1b (hour)</th>
<th>QT2a (hour)</th>
<th>QT2b (hour)</th>
<th>QT3a (hour)</th>
<th>QT3b (hour)</th>
<th>Erra (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimates (RSE %)</td>
<td>400 (0.214)</td>
<td>0.0112 (12)</td>
<td>0.00103 (7.75)</td>
<td>1.66 (1.04)</td>
<td>0.00732 (3.8)</td>
<td>0.609 (2.5)</td>
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</tr>
<tr>
<td>IV</td>
<td>0.000766 (0.107)</td>
<td>0.0838 (32.3)</td>
<td>0.0287 (24.3)</td>
<td>0.488 (26.2)</td>
<td>0.047 (40.9)</td>
<td>0.0008 (23.7)</td>
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**Numerical and visual predictive checks**

**PK model**

Parameter values and relative standard error (RSE)

<table>
<thead>
<tr>
<th></th>
<th>CL (RSE %)</th>
<th>Ka (RSE %)</th>
<th>V1 (RSE %)</th>
<th>V2 (RSE %)</th>
<th>V3 (RSE %)</th>
<th>Q2 (RSE %)</th>
<th>Q3 (RSE %)</th>
<th>Q2 (RSE %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimates (RSE %)</td>
<td>54 (0.19)</td>
<td>0.74 (0.12)</td>
<td>0.30 (10.3)</td>
<td>45 (14.6)</td>
<td>63 (28.8)</td>
<td>61 (11.7)</td>
<td>61 (12.8)</td>
<td>35 (12.8)</td>
</tr>
<tr>
<td>IV</td>
<td>0.114 (28.8)</td>
<td>0.342 (32.2)</td>
<td>0.277 (28)</td>
<td>0.020 (35.5)</td>
<td>0.143 (46.9)</td>
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</tbody>
</table>

**Example of numerical and visual predictive checks (oral single dose)**

**Design Study**

**Power of detection of drug effect:**

QT prolongation is not a parameter of our model. Therefore, we have to evaluate the value of drug effect \( \gamma \) that may cause a QTc prolongation.

\[
\gamma = 0.025 \quad \text{corresponds to a prolongation of 5 ms for a highly exposed patient.}
\]

\[
\gamma = 0.0125 \quad \text{corresponds to a prolongation of 5 ms for a normally exposed patient.}
\]

\[
1 - \beta = 95\%
\]

**Conclusion**

This work proposes a modelling and simulation based strategy in order to show QT prolongation risk is correctly assessed in the context of clinical trials in oncology. The preliminary results are very encouraging, as the power of detection of our sampling design is above 90% for clinically relevant values of drug effect. However, the assumptions underlying our approach will have to be challenged throughout developmental clinical trials.

**References**
