BAYESIAN HIERARCHICAL PK/PD MODEL TO CHARACTERIZE THE EXPOSURE-QT EFFECT RELATIONSHIP IN EARLY DRUG DEVELOPMENT

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1. Introduction
Clinical evaluation of QT/QTc interval prolongation

Introduction

- **Toxicity** (including cardiac toxicity) is a major cause of compound **attrition**

- For each compound in drug development there is a concern that it might induce arrhythmias. Reports of **cardiac arrhythmias** linked to a compound can result in its reclassification to second line status or to its withdrawal from the market.

- **Torsade de Pointes (TdP)** are rare but can lead to **Ventricular Fibrillation and death**.

- **QT prolongation**, as a **surrogate marker**, is used to assess the **risk of TdP**
Clinical evaluation of QT/QTc interval prolongation
ICH E-14 Guideline (2005)

- **The “Thorough QT/QTc Study”** (tQT)
  - Typically healthy volunteers, Placebo and positive control groups, therapeutic and supra-therapeutic doses of the test drug
  - Criteria for a negative study:
    
    When the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval ($\Delta\Delta$QTc) excludes **10ms**.
    
    - Expensive studies
    - The largest time-matched mean could be a biased estimate of the QTc prolongation effect
    - Very successful but too conservative
    - Significant false-positive trials (Hutchacher et al. 2008, Darpo et al. 2015)
Alternative approaches

- Include robust ECG assessments into early clinical trials (SAD, MAD)

- Assessment of QTc prolongation via exposure-response (ER) modelling
  - Greater understanding of the drug effect:
    - DOSE $\rightarrow$ CONCENTRATIONS $\rightarrow$ EFFECT $\rightarrow$ RESPONSE
  - Combination of different dose groups or even studies possible
  - Integration of data from measurements of all time points
2. Model-based approach for evaluation of QT prolongation
Model-based approach for evaluation of QT prolongation

Introduction

- In various publications:
  - The primary endpoint is ΔQTcF or ΔΔQTcF
  - The ER model is defined as:
    \[(Δ)ΔQTcF = \text{intercept} + \text{slope} \times \text{concentration}\]

- Population-based correction may not be appropriate for the full range of observed HR values.

References: Darpo et al. 2015, Chapel et al. 2011, Garnett et al. 2008
Introduction

- The physiological change in QT during the day (circadian effect) should also be taken into account.

- Model-based approach to discriminate drug effect from other sources of variability (heart rate change or circadian rhythm)
Model-based approach for evaluation of QT prolongation
Bayesian model

\[ QT = QT_{c0} \times RR^{\alpha} + A \times \cos\left(\frac{2\pi}{24}(t - \phi)\right) + SLOPE \times \text{exposure} \]

- **Observed variables**
  - QT (ms)
  - RR (s)
  - t (h): clock time
  - Exposure endpoint (concentration, cumulative AUC …)

- **Estimated Parameters**
  - QT_{c0} (ms/s)
  - \( \alpha \)
  - A (ms)
  - \( \phi \) (h)
  - SLOPE (ms/exposure)

  - Slope in the QT-RR relationship
  - Exponent in the QT-RR correlation
  - Amplitude in the circadian rhythm
  - Phase in the circadian rhythm
  - Slope in exposure-effect relationship

Model-based approach for evaluation of QT prolongation
Application

- Phase 1 trial for a test compound
- Parallel design
- 24 subjects: 8 placebo, 8 middle dose, 8 high dose
- Single dose followed by 2-week multiple doses
- Planned QT assessments on Day1 (pre-dose, 3, 10, 24h), Day6-Day19 (3h), Day20-21-22-26(~intake time).

Problem And Solution

To evaluate the risk of QT/QTc interval prolongation for the test compound in a non tQT study

- Estimate the exposure of the compound at QT assessment times based on a Population Pharmacokinetic model (NONMEM 7.2)
- Use a Bayesian approach to develop an ER model (R, OpenBUGS 3.2.2)
Model-based approach for evaluation of QT prolongation

Step 1: Exposure at QT assessment times

- **Depot Compartment**
  - Dose \( \cdot F_1 \)
  - \( k_a \)

- **Central Compartment**
  - \( S_2 \)
  - \( K_{20} \)

- **Peripheral Compartment**
  - \( T_{\text{max}}, T_m \)
  - \( k_{23} \)

**Solid line = Individual prediction**

Graph showing plasma concentration over time (hours) with time points marked (0, 100, 200, 300, 400, 500, 600).
Model-based approach for evaluation of QT prolongation

Step 2: Exposure endpoint and priors elicitation

**Exposure endpoint**

- Investigated exposure endpoints: plasma concentrations, cumulative exposure (AUCcumul)

<table>
<thead>
<tr>
<th>Informative priors</th>
<th>Non-informative priors</th>
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<tbody>
<tr>
<td>● Priors and hyperpriors distribution for the system-specific parameters derived from previous GRT trials and literature</td>
<td>● Non-information prior for the drug-specific parameter (slope)</td>
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</tbody>
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**Diagram notes:**

- Heart Rate (beats/min) vs. Time (hours)
- QTcF (ms) vs. Time (hours)
Model-based approach for evaluation of QT prolongation
Step 2: Results

A significant drug effect was identified, with the cumulative exposure as the exposure endpoint.

The PK/PD model allowed to estimate the drug effect at key exposure levels (posterior median and 95% credible interval).
Model-based approach for evaluation of QT prolongation
Step 2: Results

Dotted lines: geometric mean cumulative exposure at the end of the treatment phase for the middle dose and the high dose
3. Conclusion
Conclusion
Impact on the project

- This **Bayesian hierarchical PK/PD** modelling helped to **understand** the cardiac **safety** profile of the test compound.

- We could **identify and characterize the risk of potential QT/QTc prolongation** associated to the test compound, despite the limitation of the study design and collected data.

- This analysis enabled **informed decisions** with respect to the development of this compound **in an early stage of development**.
Conclusion
Future opportunities
4. References
References

- Darpo, B. et al., 2015. Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase. *Clinical Pharmacology & Therapeutics*, 97(4).
References


References


