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

Muriel Boulton | May 20, 2015

Vincent Dubois, Roberta Bursi

Development – Data Sciences – Pharmacometrics

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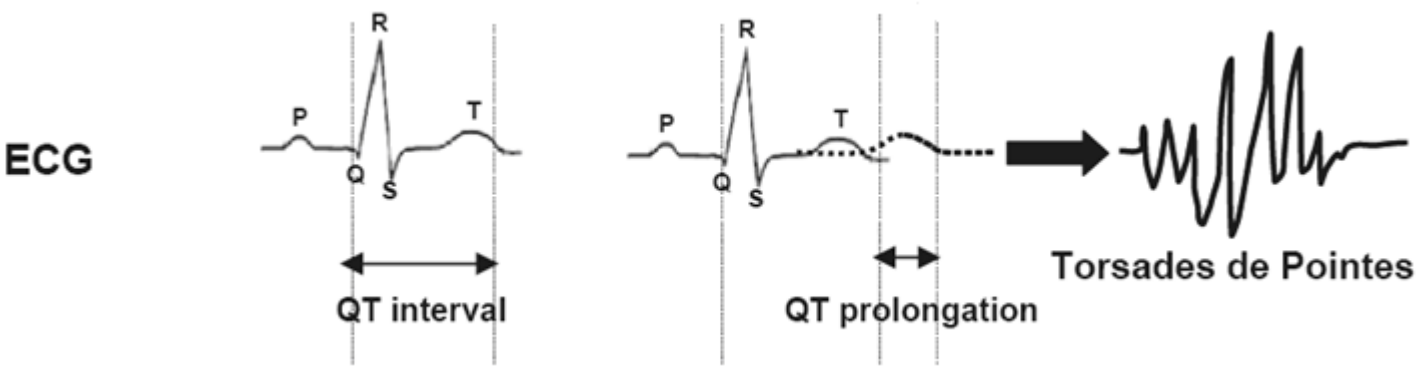
1. Introduction

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 (ΔΔQTc) 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 → **CONCENTRATIONS** → EFFECT → RESPONSE

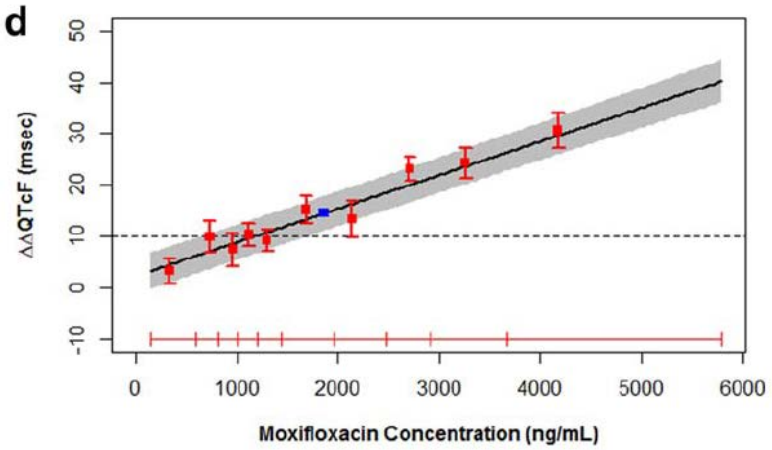
  - **Combination** of different **dose groups** or even studies possible
  - **Integration of data** from measurements of all time points

2. Model-based approach for evaluation of QT prolongation

Model-based approach for evaluation of QT prolongation
Introduction

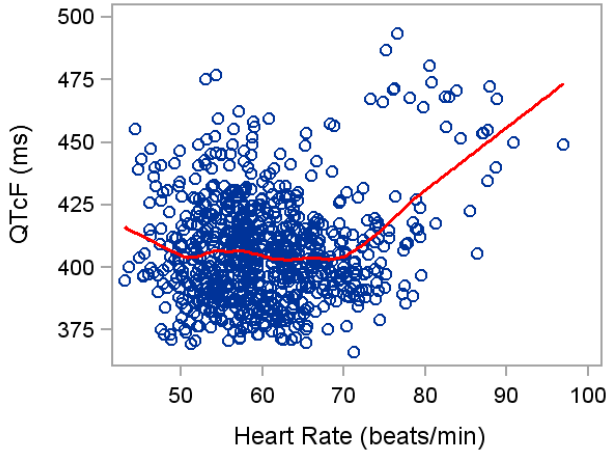
- In various publications:
  - The primary endpoint is ΔQTcF or ΔΔQTcF
  - The ER model is defined as:

  (Δ)ΔQTcF = intercept + slope * concentration



Darpo et al, CPT 2015

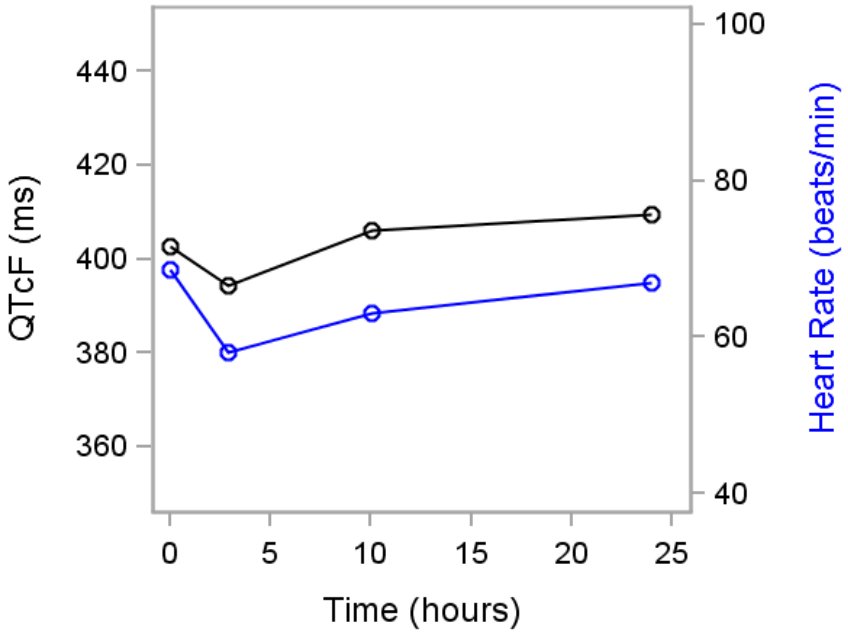
- Population-based correction may not be appropriate for the full range of observed HR values.



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

Model-based approach for evaluation of QT prolongation
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

$$QT = \underbrace{QT_{c0} \times RR^{\alpha}}_{\text{individual heart rate correction}} + \underbrace{A \times \cos\left(\frac{2\pi}{24}(t-\varphi)\right)}_{\text{circadian rhythm}} + \underbrace{SLOPE \times exposure}_{\text{exposure-effect}}$$

System specific | Drug specific

Observed variables

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

Estimated Parameters

- QT_{c0} (ms/s) → Slope in the QT-RR relationship
- α → Exponent in the QT-RR correlation
- A (ms) → Amplitude in the circadian rhythm
- φ (h) → Phase in the circadian rhythm
- SLOPE (ms/exposure) → Slope in exposure-effect relationship

References: Piotrovsky 2005, Chain A.S.Y & Dubois V.F.S. et al. 2013, Dubois et al. 2014

Model-based approach for evaluation of QT prolongation
Application

Context

- 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).

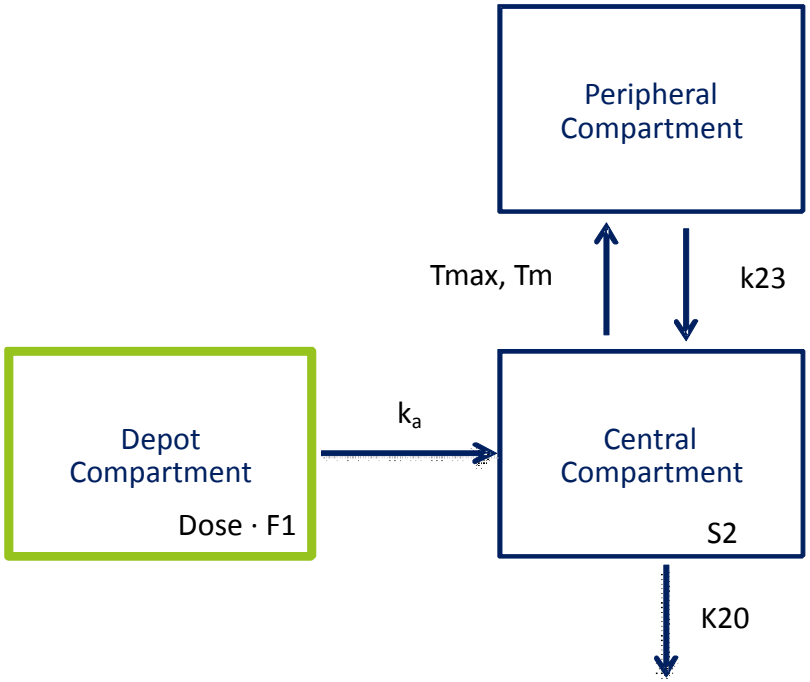
Problem And Solution

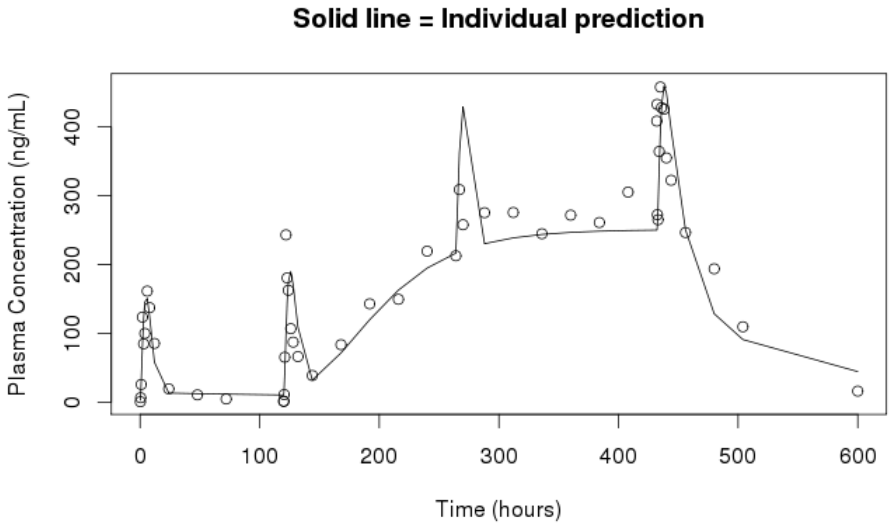
To evaluate the risk of QT/QTc interval prolongation for the test compound in a non tQT study

- 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

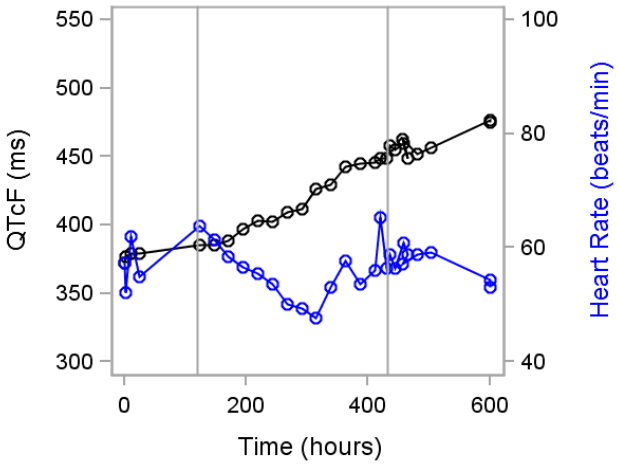
Step 1: Exposure at QT assessment times





Model-based approach for evaluation of QT prolongation
Step 2: Exposure endpoint and priors elicitation

Exposure endpoint



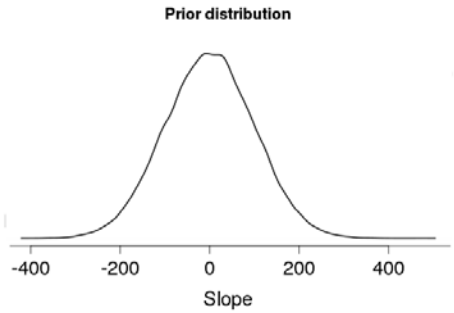
Exposure endpoints investigated: plasma concentrations, cumulative exposure (AUCcumul)

Informative priors

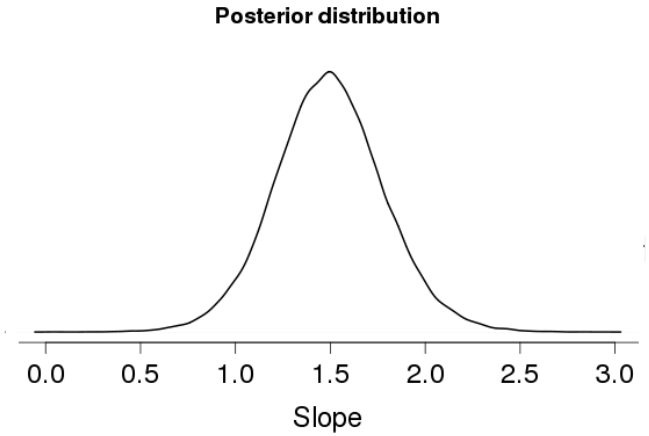
- Priors and hyperpriors distribution for the system-specific parameters derived from previous GRT trials and literature

Non-informative priors

- Non-information prior for the drug-specific parameter (slope)

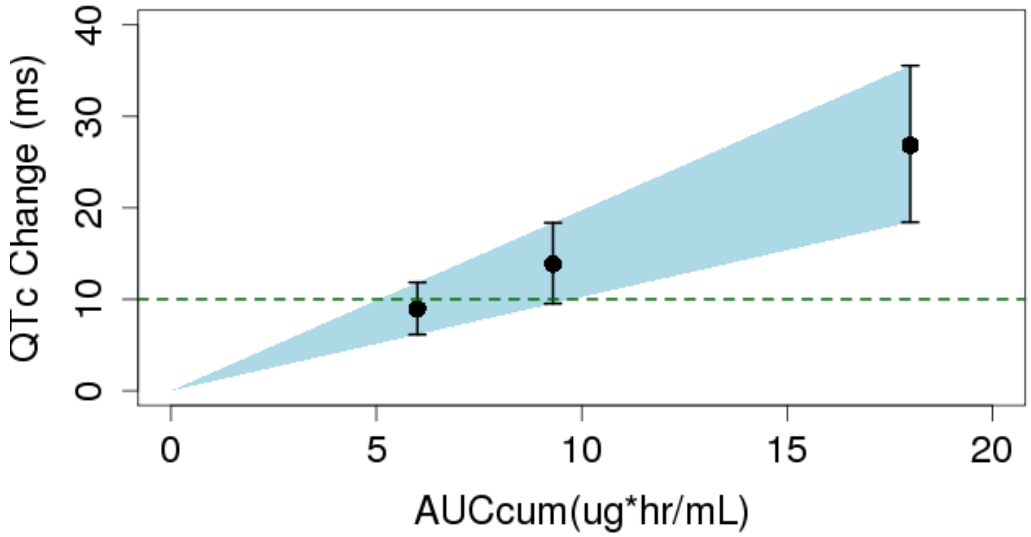


Model-based approach for evaluation of QT prolongation
Step 2: Results



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
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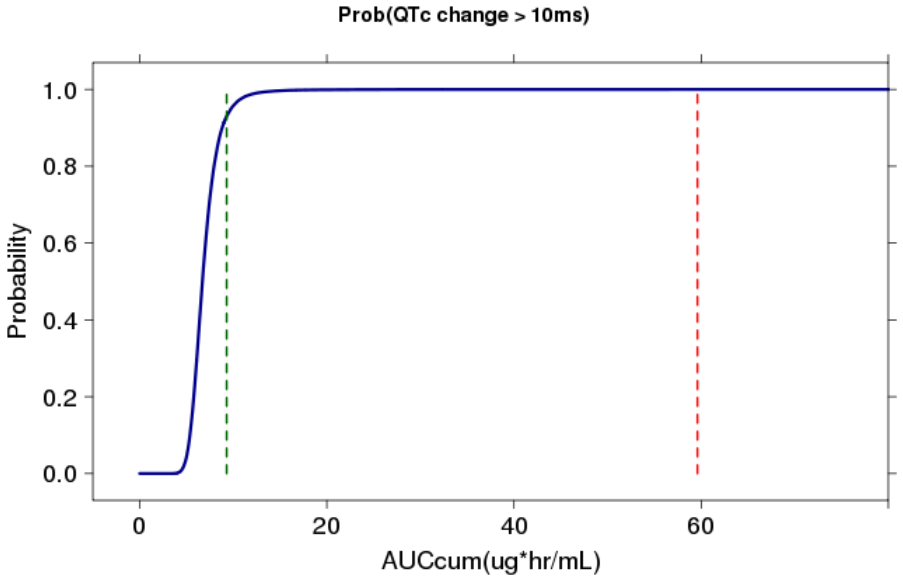
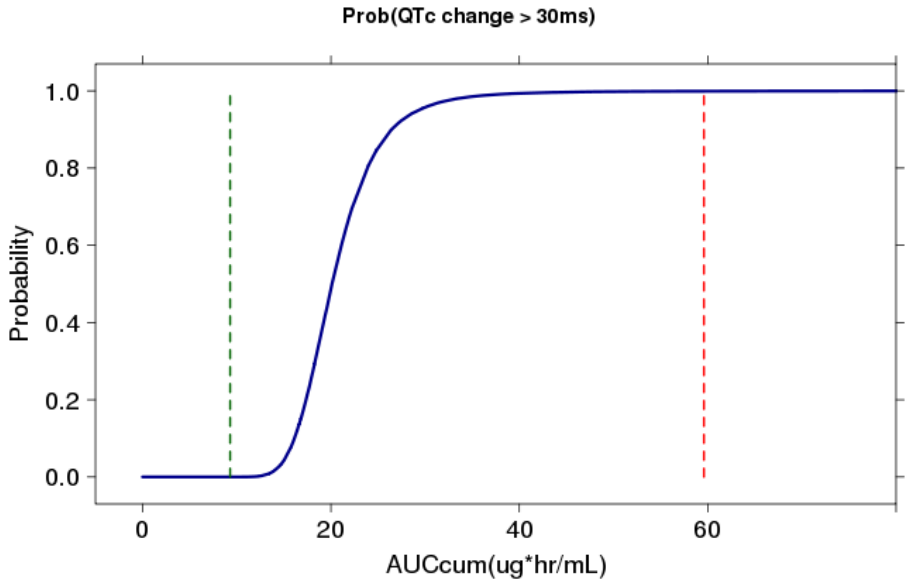




Dotted lines: geometric mean cumulative exposure at the end of the treatment phase for the middle dose and the high dose

3. Conclusion

Conclusion

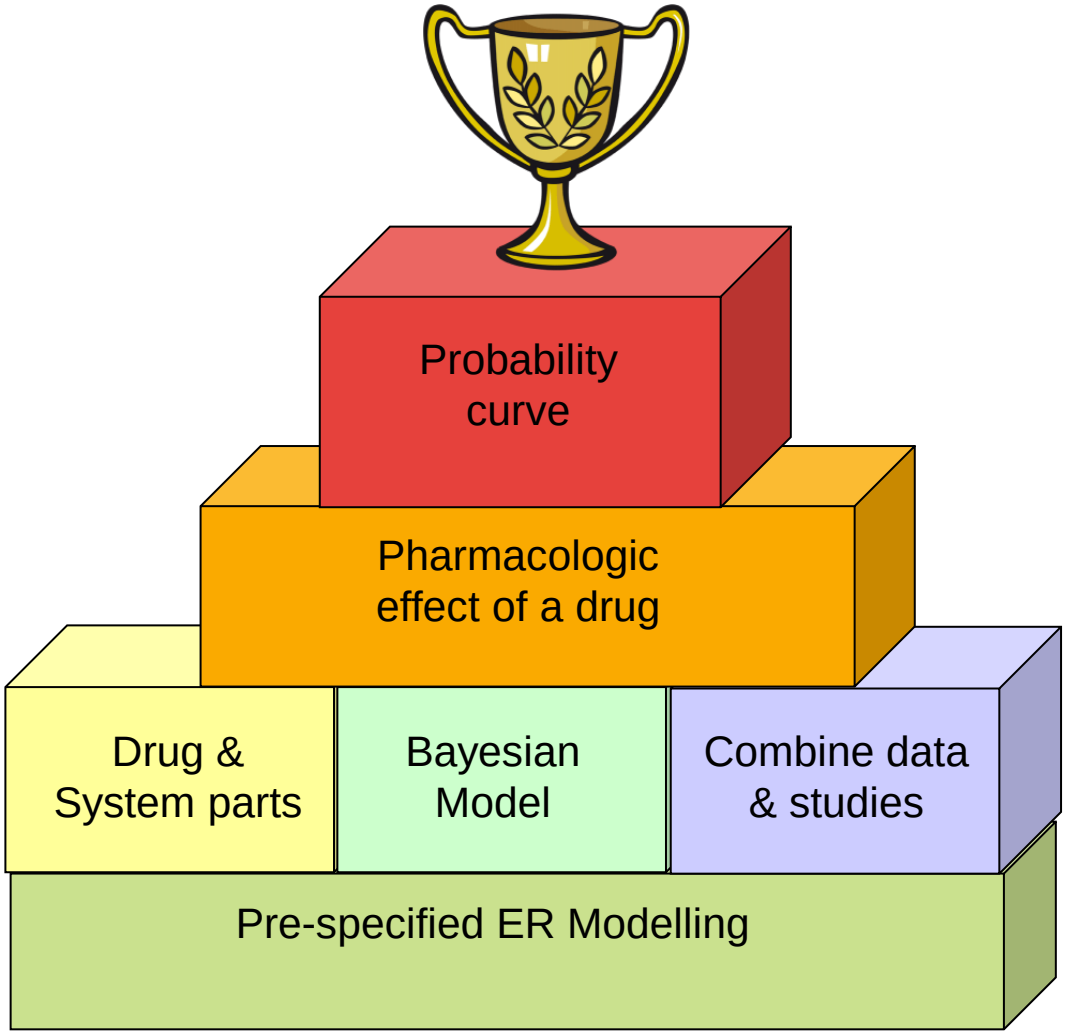
Impact on the project

- 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



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