

A streamlined, semi-automated workflow allows quick and efficient QTc and other ECG intervals modelling assessment, saving time and cost.

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Abstract

A semi-automated workflow for concentration-response modelling of QTc was developed in AstraZeneca, which is fully aligned with the regulatory requirements. This workflow increased efficiency of this standard modelling assessment and lead to significant time and cost savings. The workflow involves templates for the analysis plan and report, dataset standards, and R scripts for data formatting, modelling, prediction, and output generation. The workflow has been successfully developed, validated, and used to conduct C-QTc assessments for several drugs in AstraZeneca portfolio, eliminating the need for dedicated TQT studies and extensive ECG monitoring in phase 3.

Introduction

- All drugs with systemic bioavailability need assessment of the QT interval by ECG in clinical trials to rule out risk of QT prolongation and Torsade de Pointes [1]
- Historically, this required a costly (\$1-4 million) Thorough QT (TQT) study before start of phase 3.
- Currently, this assessment includes C-QTc modelling using digitally recorded ECG data from early phase studies
- Technical requirements for the C-QTc modelling assessment are clearly defined in the Scientific White Paper [2], published by FDA and endorsed by the ICH E14 guidance [3]

Methods

- The Clinical Pharmacology department at AstraZeneca, together with AstraZeneca Cardiac Safety Knowledge Group, developed a semi-automated workflow for C-QTc analysis (Figure 1)
- This workflow involves templates for the modelling analysis plan and report, dataset standards, and R scripts within a GxP compliant pharmacometrics environment (Metworx and Github Enterprise)



Standardized R scripts

- A set of 10 R scripts was developed, to perform exploratory data analysis, modelling, and generate all required outputs
- Semi-automated reporting was incorporated using flextable and officer packages, where outputs from R are automatically added into relevant sections of the report
- All scripts were QCed and validated
- pkgr was used for R package management

Dataset Standard

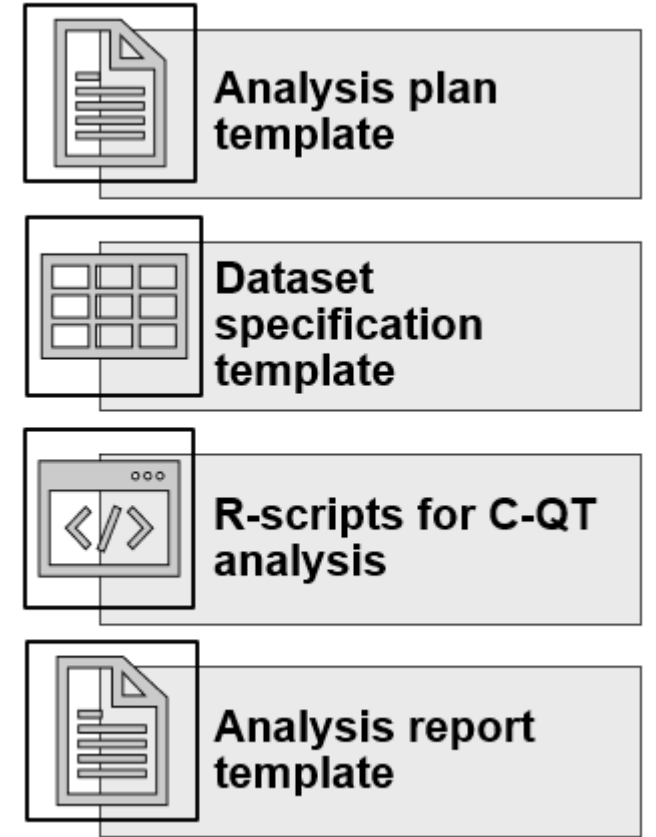
Standardized dataset was a crucial part in developing the workflow; currently, the same dataset structure is used for each C-QT assessment, (i.e., using the same variable names) which is aligned with developed R scripts.

Templates for analysis plan and report

Word templates were developed for Analysis Plan and Analysis Report; the templates include all necessary sections required by the Regulatory Agencies, such as checks of assumptions using exploratory plots, details of ECG collection.

Results

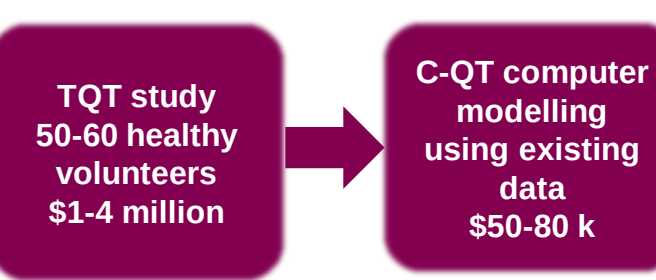
Figure 1. C-QT modelling workflow developed in AstraZeneca



Cost saving

- \$50-80k with modelling vs \$1-4M with TQT study per project
- Assuming 3-4 projects seeking regulatory endorsement per year (ahead of phase 3), this will provide savings of up to \$16 million a year.

Figure 2. Old and new approaches to assess risk of QT prolongation



Time saving

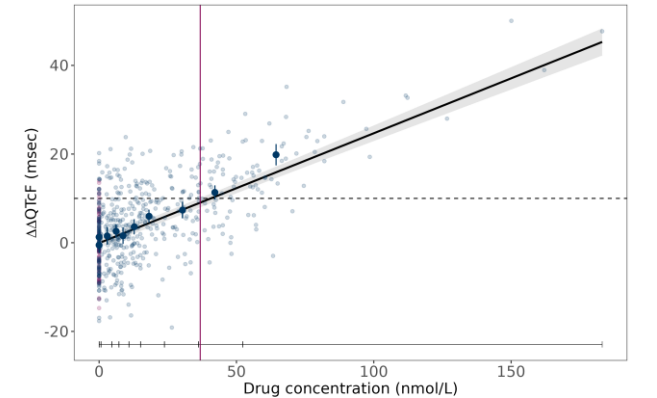
- By applying model-based assessment we avoid potentially long dedicated TQT study later in drug development
- By using the developed semi-automated workflow, the modelling assessment is fast and efficient:
 - no need to write new code
 - minimal QC required since standard scripts are used

Alignment with Regulatory Agencies requirements

The set of R scripts developed in this workflow generate all outputs required as a part of clinical QT assessment, outlined in the Scientific White paper [2]; this includes for example:

- hysteresis plot
- table of QT/QTcF outliers (i.e. observations where QT/QTcF reaches certain thresholds, for example >450 mg)
- model predictions for the concentration(s) of interest, for example high clinical scenario (Figure 3)

Figure 3. Example of a standard output for C-QT Report



Successful validation

- Multiple C-QT assessments were conducted using the developed QT framework during last few years and were successfully approved by FDA (and other Heath Authorities), including:
- AZD8233, antisense oligonucleotide targeting PCSK9 [4]
 - Capivasertib, small molecule, AKT serine/threonine protein kinases [5]
 - Mitiperstat, small molecule, myeloperoxidase inhibitor [6]

Conclusions

- A semi-automated C-QTc analysis workflow was successfully developed in AstraZeneca, fully reproducible and aligned with Regulatory Agencies' requirements.
- Several C-QTc reports generated using this process were successfully approved by Regulatory Agencies and the workflow is now used routinely for all C-QTc assessments across AstraZeneca portfolio.
- The development and implementation of this workflow have led to significant cost, time, and resource savings.

References

[1] E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Guidance for Industry. 2005
[2] Garnett et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397
[3] E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Questions and Answers (R3) Guidance for Industry. 2017
[4] Rekić et al. AZD8233 antisense oligonucleotide targeting PCSK9 does not prolong QT interval. Br J Clin Pharmacol. 2022;88(11):4839-44
[5] Voronova et al. Concentration-QT modelling shows no evidence of clinically significant QT interval prolongation with capivasertib at expected therapeutic concentrations. Br J Clin Pharmacol. 2022;88(2):858-64
[6] Parkinson et al. The myeloperoxidase inhibitor mitiperstat (AZD4831) does not prolong QT interval at expected therapeutic doses. Pharmacology Research & Perspectives 2024;12:e1184