

Leading with Excellence: The Impact of Model-Based QT Assessment in Drug Development

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Introduction

- All drugs with systemic bioavailability require assessment of the QT interval, which represents ventricular depolarization and repolarization activity of the heart by electrocardiogram (ECG) in clinical trials [1].
- Historically, clinical QT assessment has been performed in dedicated thorough QT/QTc (TQT) studies, which can be expensive and complex. Since 2015, C-QTc (concentration response) modelling was approved as a primary analysis method [2].
- Since then, AstraZeneca (AZ) evaluated innovative ways to implement this new regulatory guidance in assessing the risk of QT-prolongation in a patient-centric and cost-effective way.

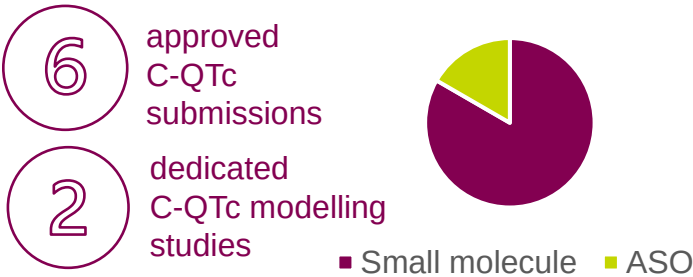
Methods

- AZ swiftly adapted to the new regulatory landscape, instituting a structured framework for project teams to apply these methodologies effectively [3].
- Modeling experts were included in the Cardiovascular Safety Knowledge Group (CV SKG) to support model-based assessment.

Successful C-QTc approvals

Since 2015, AZ had 6 approved FDA submissions based on C-QTc modeling of existing data (e.g., SAD/MAD). Sample size varied between 40-180 participants; all submissions were based on a single study [4-7].

Figure 2. Summary of approved C-QTc submissions and dedicated C-QTc modeling studies since 2015.



All internal C-QTc modeling assessments utilize a standardized framework that includes standard R scripts for complete modeling assessment, alongside templates for analysis plans and reports. These templates are highly pre-populated and can be auto-populated with outputs generated by the R scripts [3]. This ensures that our C-QTc reports are consistent and fully aligned with regulatory guidelines and recommendations.

Cardiovascular Safety Knowledge Group

AZ CV SKG is a cross-functional network of individuals, including pre-clinical, clinical, modeling and translational safety experts. They provide guidance on the CV related issues, including support for QT assessment strategies. By including modelling experts in the group, we ensure that project teams can receive guidance and support with C-QTc assessment and our knowledge and experience can be shared across the portfolio.

Figure 3. AZ Cardiovascular Safety Knowledge Group and modeling-related support.

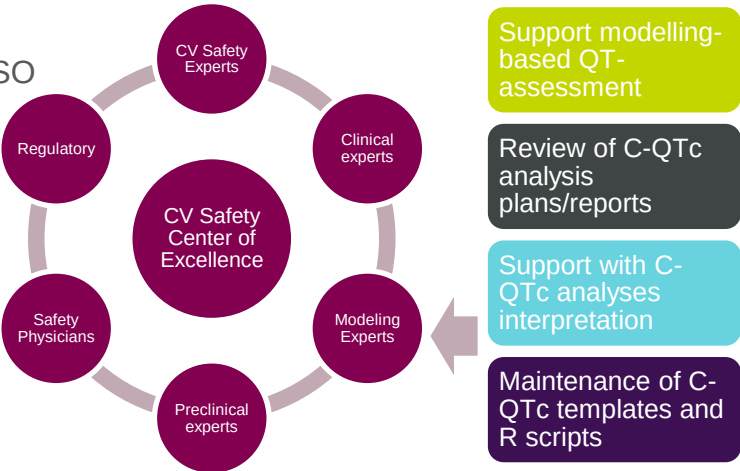
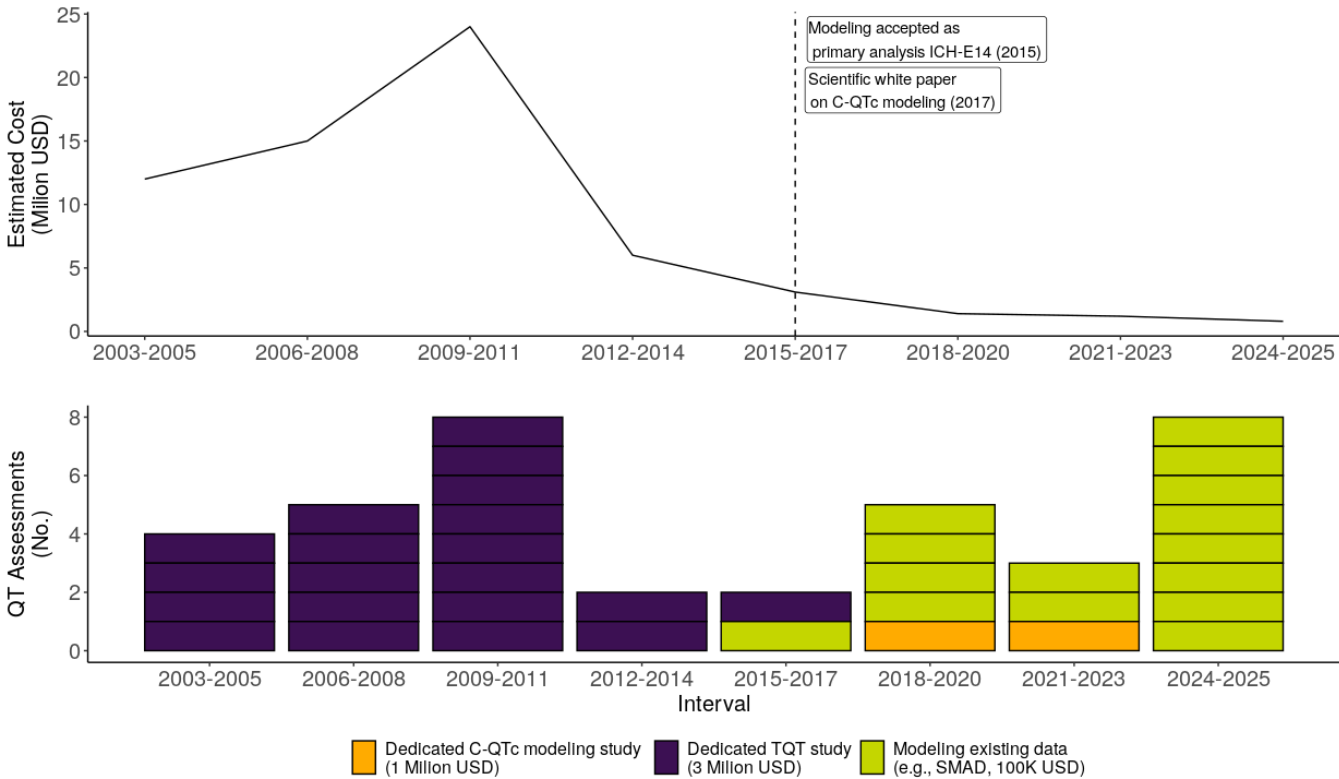


Figure 1. Summary of clinical QT assessments conducted in AstraZeneca between 2003-2025.



The cost of a (historical) dedicated TQT study can vary, depending on its design, but in general it is expected to be within the range of 2-4M USD. We used cost of 3M in the summary above. Similarly, the cost of a dedicated CQT modeling study can vary, but in general it is lower than a historical TQT study (here, we assume 1M USD). The cost of C-QTc modeling of existing ECG data can also vary, depending on the internal FTE cost or cost of an external consultant.

- Our prompt response facilitated consistent application of the C-QTc methodology across our entire portfolio: currently all clinical QT assessments in AZ are conducted using C-QTc modelling approach.

Results

Reducing cost of clinical QT assessment

Using ECG data collected from early studies instead of a dedicated TQT study reduced the cost of clinical QT assessment by up to 98%. Figure 1 shows a dramatic reduction in cost at AZ since the ICH E14 approval of C-QTc modelling in 2015 and the adaptation of the new methodology by AZ.

Dedicated TQT studies with C-QTc modeling

Since C-QTc modelling was approved as a primary analysis method (as an alternative to the historically used by-time-analysis with Intersection Union Test), AZ conducted 2 dedicated TQT studies using the new approach [8,9]. Both were single-dose, cross-over studies, with a sample size of 24 (over 50% size reduction compared to a historical TQT study, typically with 50-60 subjects). In one of the studies, we used the immediate-release formulation (as an alternative to extended-release formulation used in the planned commercial product) to achieve supratherapeutic exposures and thus avoided positive control and further simplified the dedicated C-QTc study [8].

High quality ECGs for C-QTc modeling

An important requirement for using C-QTc modeling is collection of high quality ECGs. In AZ, we have an internal ECG Core Laboratory (AZ ECG Centre), established in 2003 and based in Gothenburg, Sweden. The Centre supports management and blinded analysis of digital ECGs from early clinical studies conducted all over the world. By utilizing internal ECG Centre, this allows AZ to efficiently collect and manage high quality ECGs, used later in C-QTc model-based assessments.

Conclusions

- The swift adaptation to the new regulatory opportunity allowed AZ to excel in using model-based QT assessment in drug development.
- This not only largely reduced the cost of clinical QT assessment (up to 98%) and saved time but also avoided unnecessary exposure of healthy volunteers to the drug (by avoiding dedicated TQT studies).
- Internal CV SKG ensures that project teams across whole AZ portfolio can access expert support for their QT assessment strategy.

Acknowledgements

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