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A Programmer's Insight into an Alternative to TQT Study Data Submission

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ABSTRACT

We detail the submission process for Phase I concentration-QTc data to regulatory agency, seeking an alternate approach from conducting a separate Thorough QT/QTc (TQT) study. A waiver from the TQT is significant because it saves time by not requiring a separate study, which is critical to getting therapies to patients faster. The submission datasets to support the QT evaluation align with the FDA Technical specifications document for Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs and CDISC TAUG-QT standards. The submission package also adheres to the FDA Technical Conformance Guide and QT Evaluation Report Submission checklist.

This paper delves into the creation of a submission package utilizing Continuous Holter ECG and PK data from Phase I randomized placebo-controlled dose escalation studies. It details the necessary updates required for the SDTM trial design data sets, along with inclusion of necessary SDTM/ADaM domains that are pertaining to the QT submission and specific to the cohorts included in the cardiac safety analysis. In addition, amendments to the aCRF, define.xml and reviewer's guide will be described in this paper, that provides valuable insights into the intricacies of creating a comprehensive submission package for consideration of an alternate approach to the TQT study.

INTRODUCTION

The development of new therapies requires rigorous evaluation of their cardiac safety profile, including assessment of their potential to prolong the QT interval, a measure of cardiac repolarization. While the Thorough QT/QTc (TQT) study is the standard regulatory requirement for evaluating QT interval prolongation, securing a waiver from this study holds the potential to significantly expedite the drug development process. Recording and analyzing electrocardiograms (ECGs) with stringent quality control as in a TQT study, could feasibly be integrated into first-in-human or dose escalation studies. This proactive approach to assessing QTc prolongation during Phase I clinical development enables informed decision-making at an early stage of the clinical drug development timeline. When appropriately designed and executed, early phase QT assessments can provide sufficient evidence of QT effects to substantiate regulatory submissions. This paper aims to provide a detailed overview of the submission process for Phase I concentration-QTc data to regulatory agencies, focusing on the creation of a comprehensive submission package to support an alternate approach to the TQT study.

REGULATORY BACKGROUND

REGULATORY GUIDANCE

The regulatory framework governing our submission encompasses ICH E14 guidelines, CDISC TAUG-QT standards, and FDA Technical Specifications, among others. The following guidelines provide a roadmap for evaluating cardiac safety and QT interval prolongation, essential for the regulatory review process.

- **ICH E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs:** The ICH E14 is a regulatory guideline that provides recommendations for the design, conduct, analysis, and interpretation of clinical studies aimed at evaluating the potential of non-antiarrhythmic drugs to prolong the QT interval and induce cardiac arrhythmias, particularly Torsade de Pointes (TdP).
- **E14 and S7B Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential - Questions and Answers:** The Q&A document serves as a supplementary resource to clarify key aspects of the ICH E14 and S7B guidelines. Of note is that this document provides further guidance on the use of concentration response modeling of QTc Data as an alternative to the TQT study.

- **CDISC TAUG-QT Standards:** The CDISC Therapeutic Area User Guide (TAUG) for QT (QT/QTc) Studies provides guidance on the standardized representation of QT interval data in clinical trial datasets. It includes guidelines for data collection, tabulation, and analysis, ensuring consistency and interoperability across different studies and sponsors.
- **FDA Technical Specifications Document for Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs:** The FDA QT Evaluation Technical Specifications Document provides detailed guidelines and specifications for submitting datasets related to QT/QTc interval evaluation in clinical trials. It outlines requirements for data formatting, structure, and content to ensure consistency and compatibility with FDA review process.
- **QT Evaluation Report Submission Checklist:** The QT Evaluation Report Submission Checklist is a tool provided by the FDA to assist sponsors in preparing and submitting QT evaluation reports as part of regulatory submissions. The checklist outlines key components and information required in the QT submission such as the evaluation report, statistical analysis plan, datasets, programs, ECG waveforms etc. It serves as a guide for sponsors to ensure completeness and accuracy in their submissions.

By adhering to these guidelines and standards, sponsors can ensure consistency, transparency, and regulatory compliance in their submissions to the FDA, facilitating the review and evaluation of the cardiac safety of the investigational drug.

ALTERNATIVES TO THE TQT STUDY

As per ICH E14 Q&A, the following should be considered when substituting for the TQT study:

Data Sources: Concentration-response data can be obtained from various studies, including first-in-human studies and multiple-ascending dose studies. The concentrations achieved should exceed those at the maximum therapeutic dose at steady-state, reflecting high clinical exposure scenarios such as drug interactions or organ dysfunction. Wide dose ranges in early-phase studies are encouraged to characterize effects at high concentrations.

Quality Control: Data analysis should meet the same quality standards as a dedicated QT study, including robust ECG recording and analysis to support valid ECG interval assays, as outlined in the ICH E14 guidance.

Pooling Studies: If pooling ECG interval data from multiple studies is intended, it is crucial to test for heterogeneity and discuss potential biases in the analysis plan.

Positive Control: A separate positive control is not necessary if either: a) the response is characterized at a sufficient multiple of high clinical exposure, or b) if high clinical exposure is achieved but sufficient multiple is not obtained for various reasons then a nonclinical integrated risk assessment can be used as supplementary evidence. Adequate justification for not testing higher doses should be provided, including evidence from hERG assays and in vivo assays per ICH S7B guidelines.

DATASETS FOR QT STUDIES

The ECG Test Results (EG) domain collects both Quantitative ECG data (e.g., HR, PR interval, QRS, absolute QT interval, and QTc) and Qualitative ECG data (e.g., descriptive findings based on visual interpretation of the waveforms).

For studies utilizing advanced statistical methods for QT interval correction, the correction formula and model coefficients used by these methods need to be submitted. According to TAUG-QT1.0, if the QTc data is provided by the vendor, it is mapped to the SDTM ECG QT Correction Model Data (QT) domain. Conversely, if the sponsor conducts the QT correction, sponsor-derived data should be submitted in the ADaM Analysis Dataset for ECG QTc Model Data (ADQT) domain. Simple population correction formulas like Fridericia's or Bazett's do not require submission using QT/ADQT domains.

Device Domains are employed to gather information about the types of devices utilized for recording and processing Continuous ECG data.

The Comments (CO) domain may be included to map comments collected during the Continuous ECG collection and analysis.

The Analysis Dataset for Electrocardiogram Tests (ADEG) comprises a comprehensive set of variables related to the subject and their quantitative measures in the ECG and ECG interpretation statements. Additionally, the FDA QT-TCG lists additional variables necessary to aid FDA review beyond those listed in the TAUG-QT.

The Pharmacokinetic Concentrations Analysis Dataset (ADPC) includes a comprehensive set of variables related to the subject and their quantitative PK measures. It can be a subset of the CSR ADPC dataset allowing for concentration-ECG changes analysis (e.g., concentration-QT). Consistency in coding variables present in both ADEG and ADPC is crucial for proper mapping of time-matched PK and ECG rows. Although a subset of ADPC, it also encompasses additional variables and specific derivations.

The Analysis Dataset for ECG QTc Model Data (ADQT) contains heart rate correction-related information if the ADEG dataset includes heart rate corrected QT (QTc) values obtained using a formula and coefficients derived by the sponsor or vendor. Vendor-supplied data mapped to SDTM QT may be carried forward into ADQT, contingent upon the sponsor's requirements.

PREPARATION FOR THE SUBMISSION

STUDY BACKGROUND

This paper outlines the process of assembling a submission package seeking an alternate approach to the TQT study, using the data obtained from a Phase I, Randomized, Double-blind, Placebo-controlled Study evaluating the Safety and Pharmacokinetics of Single and Multiple Ascending Doses (MAD) of the Investigational Drug in Healthy Subjects. Additionally, the study aimed to investigate the effects of the Investigational Drug on QTc interval in healthy subjects. The continuous ECG monitoring was performed only in the Multiple Ascending Dose cohorts of the study. Doses at sufficient multiple of high clinical exposure were investigated in the study.

Continuous electrocardiogram (ECG) monitoring was conducted using a continuous 12-lead digital recorder, allowing for precise extraction and analysis of QTc measurements from ECG replicates. These data were then utilized to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship between plasma concentration of the Investigational Drug and QTc interval. To ensure thorough QT analysis, a distinct analysis plan was devised specifically for the evaluation of continuous ECG assessments and concentration-QTc analysis. A dedicated QT evaluation report was created to support the submission of an alternate approach to the TQT study.

A central ECG laboratory vendor played a pivotal role, providing essential support for continuous ECG acquisition, over-reading, analysis, and reporting. The SDTM and ADaM datasets, and QT evaluation report was created by the central ECG vendor. Subsequently, the sponsor assembled the submission package using the deliverables from the Continuous ECG vendor along with the datasets prepared for the CSR.

SUBMISSION COMPONENTS

As described in the regulatory guidance section, submission of QT evaluation report included the data package components that are aligned with the QT evaluation report checklist. Datasets package includes both the SDTM and ADaM data package components. To support the review of QT evaluation report and to ensure traceability and contextual relevance for the reviewer, relevant SDTM domains were submitted in the data package. These domains consist of the Trial domain datasets, Demographics (DM), Disposition (DS), Subject Visits (SV), Subject Elements (SE), Exposure (EX), ECG Test Results (EG), Comments (CO), Pharmacokinetic Concentrations (PC), and Vital Signs (VS). SDTM domains were updated to include the data only for the cohorts that were planned per protocol for the QT evaluation. Similarly, the Trial Arms, Trial Elements and Trial Summary datasets were revised as necessary

encompass only the cohorts involved in the QT evaluation. In addition, Trial summary dataset was updated to integrate QT-specific parameters.

Table 1 provides the list of QT-specific parameters to be included in the Trial summary (TS) domain.

TSPARMCD	TSPARM	CDISC Definition
EGBLIND	ECG Reading Blinded	Indicates whether assessors of ECGs for this study were blinded to subject identity, timing, and treatment.
EGCTMON	ECG Continuous Monitoring	Indicates whether the 10-second ECGs for this study were extracted from a continuous recording.
EGLEADPR	ECG Planned Primary Lead	The ECG lead which was planned to be used for ECG interval measurements for this study.
EGLEADSM	ECG Used Same Lead	Indicates whether all ECG interval measurements for the study were based on the same lead.
EGRDMETH	ECG Read Method	The degree of automation involved in assessing the ECGs for this study.
EGREPLBL	ECG Replicates at Baseline	Indicates whether this study includes replicate ECGs for time points during the baseline portion of the study.
EGREPLTR	ECG Replicates On-Treatment	Indicates whether this study includes replicate ECGs for time points during the on-treatment portion of the study.
EGTWVALG	ECG Twave Algorithm	The algorithm used to identify the end of the T wave for ECGs for this study.
CTAUG	CDISC Therapeutic Area User Guide	The name and version of the CDISC therapeutic area user guide that is being used in the study submission.
FDATCHSP	FDA Technical Specification	The name and version of the FDA technical specification that is being used in the study submission.

Table 1. Trial Summary Parameters for QT submission

The following table (Table 2) provides examples of other Trial summary parameters that may need to be updated depending on the QT evaluation analysis. If only a subset of the study cohorts is included for the QT evaluation, then the corresponding parameters need to be revised accordingly.

TSPARMCD	TSPARM	CDISC Definition
SPREFID	Sponsor's Study Reference ID	The reference identifier by which the study is known to the sponsor. This may be different from the STUDYID if the data were collected under a different identifier (e.g., used in a situation where a contract facility performs the study and provides a final report).
ACTSUB	Actual Number of Subjects	Actual number of subjects enrolled; may include subjects who were not randomized.
DOSE	Dose Level; Dose per Administration	The amount of study drug (or placebo) administered to a patient or test subject to be taken at one time or at stated intervals.
DOSFRQ	Dosing Frequency	The number of doses administered per a specific interval.

TSPARMCD	TSPARM	CDISC Definition
NARMS	Planned Number of Arms	The planned number of intervention groups.
NCOHORT	Number of Groups/Cohorts	The number of groups or cohorts that are part of the study.

Table 2. Additional Trial Summary Parameters updated for QT evaluation submission.

Annotated (aCRF) was created by annotating only the study CRF pages specific to the domains and cohorts that were submitted in the QT evaluation package. CRF fields that corresponded to domains or cohorts that were not submitted in the data package were annotated as “NOT SUBMITTED”.

ADaM data sets included Subject Level Analysis Dataset (ADSL), ECG Analysis Dataset (ADEG), PK Concentrations Analysis Dataset (ADPC). The QT evaluation analysis was exclusively performed on a subset of the cohorts, and ADaM datasets for submission included only subjects from those cohorts.

Define.xml was generated to provide a standardized definition of the structure and content of datasets utilized in the QT evaluation package, serving as a companion document to clinical trial data submissions to ensure consistency, transparency, and interoperability. It details the origin and derivation of the variables in both SDTM and ADaM domains. The inclusion of only a subset of the study cohorts for continuous ECG monitoring also necessitated updates in codelists (e.g. ETCD, ARMCD, EXDOSFRQ etc.) and source reference CRF page numbers. In accordance with the technical specification guidance document, to provide traceability between SDTM and ADaM data sets, and support the reviewer analysis, specifications ensure that the standard controlled terminology and sponsor-defined controlled terminology were used consistently across the data sets.

The Study Data Reviewer's guide (csdrg) was included to provide context for tabulation datasets and terminology that benefit from additional explanation beyond the define.xml. The reviewer’s guide provided additional details about the domains that are included in the submission package along with the rationale for their inclusion. Furthermore, in the conformance summary, the reasons for omission of certain domains from the package was explained, along with explanations for other conformance issues.

Analysis Data Reviewer's guide (adrg) was developed based on the QT analysis plan, it included detailed explanations of the derivations performed in ADEG and ADPC. This detailed documentation provides reviewers with comprehensive insights into the methodologies employed and the rationale behind the data transformations, derivations of flag variables and analyses. Variable conventions for the flag variables along with the derivation methods are thoroughly documented. For ADEG data set, additional details in relation to the QT evaluation primary and secondary objective are documented listing the parameters and their relation to the end points of the QT evaluation. The “Submission of Programs” section of Analysis Data Reviewer's guide lists all the Tables, Listings, and Figures included in the submission package.

Once all the individual components are ready, the submission package is assembled as instructed in the FDA TCG as in the Figure 1. In addition, the ECG waveforms are to be uploaded under m5 -> datasets -> [study] -> misc -> aecg.

During the preparation of the submission, the QT Evaluation report submission checklist is used as a guide to check and confirm that all the necessary components are included in the package. Once the package is assembled, the tables in the checklist are filled out to include the locations and links to the individual components, aiding in the review of the submission.

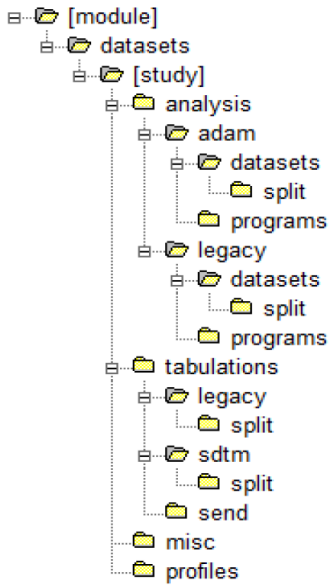

Figure 1. Submission folder structure for study datasets

CONCLUSION

In conclusion, this paper has provided a detailed account of the process involved in assembling a submission package seeking an alternate approach to the TQT study for regulatory review, addressing the associated challenges and the strategies employed to overcome them while ensuring accuracy, transparency, and regulatory compliance. Collaboration with central ECG laboratory vendors and adherence to regulatory guidance and standardized datasets are instrumental in streamlining the submission process and expediating review by regulatory authorities.

Furthermore, the documentation provided in the submission package, such as the Define.xml, Study Data Reviewer's guide and Analysis Data Reviewer's guide, serves as invaluable references for the reviewers, offering detailed insights into dataset structures, variable definitions, and analysis methodologies. Tailoring these documents to accurately reflect the content of the submission is of utmost importance.

In essence, the assembly of a submission package for an alternate approach to the Thorough QT/QTc study represents a pivotal milestone in the journey of bringing novel therapies to market, effectively saving time and costs crucial for delivering therapies to patients faster.

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