Phenomenex QT+ Cardiac Safety Evaluation Software

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**INTRODUCTION**

- QT interval is the duration of ventricular depolarization and subsequent repolarization
- Certain drugs can delay cardiac repolarization, as measured by prolongation of the QT interval on the surface electrocardiogram (ECG)
- Extensive QT interval prolongation is a biomarker for a potentially life-threatening cardiac arrhythmia called torsade de points (TdP)
- Delayed cardiac repolarization and the clinical risk for TdP has resulted in removal of marketed drugs

Pharsight’s Phoenix QT+ software provides data processing and modeling tools to address whether a drug prolongs cardiac repolarization as specified in ICH E14 guidelines. It can be used to analyze ECG and PK data for both regulatory submissions and for internal decision making. The data analysis workflow is built as part of the Phoenix software platform, which integrates with software such as Phoenix WinNonlin for NCA and individual modeling, NLME for population analysis, and AutoPlot for report generation.

The available QT+ workflow objects are the following:
- Heart Rate Correction
- QT Transformations to obtain corrected QT interval (QTC)
- Central Tendency Analysis and Assay Sensitivity
- Summary Reporting and Outlier Analysis
- Exploratory Plots
- Concentration-QT Modeling

**ICH E14 Guidelines**

The International Conference on Harmonization (ICH) issued the E14 Guidelines to address QT interval prolongation in drug development. These are followed by regulatory agencies in the US, Europe, and Japan. The centerpiece of the ICH E14 Guidance is the thorough QT (TQT) study:

- Regulatory threshold is around 5 ms
- Central Tendency Analysis and Assay Sensitivity
- Summary Reporting and Outlier Analysis
- Exploratory Plots
- Concentration-QT Modeling

Results guide intensity of ECG monitoring during subsequent drug development.

Phoenix QT+ is designed to easily perform analysis as specified in the ICH E14 Guidelines.

**Phoenix QT+ Workflow**

Heart Rate Correction:

- Bazett: QTb = QT/RR\(^{1.5}\)
- Fridericia: QTcF = QT/RR\(^{0.33}\)

**QT Transformation:**

<table>
<thead>
<tr>
<th>QT Transformation</th>
<th>QTcF, ms</th>
<th>Baseline QTcF, ms</th>
<th>QTcF, ms</th>
<th>ΔQTcF, ms</th>
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</table>

**Central Tendency Analysis:**

Least-square mean differences for supra-therapeutic dose of test drug

- ΔQTcF, ms
- PR Interval
- QRS Interval
- Heart rate

**Outlier Analysis:**

Multiple limit values reported, due to lack of consensus

- QT/QTc Interval
- ΔQTc Interval
- PR Interval
- QRS Interval
- Heart rate

**Concentration - QT Modeling:**

- Bootstrapped QT predictions at concentrations of interest; e.g., at Cmax values from renal impairment study

**SUMMARY**

Phoenix QT+ software streamlines the analysis of data from thorough QT studies. It implements the recommendations in the ICH E14 Guidelines for QT/QTc analysis, and outputs calculations and plots needed for both internal decision making and for regulatory submissions. The interface for QT+ is the same user-friendly GUI as Phoenix WinNonlin and other Phoenix tools, which decreases the time needed to learn the software.

**REFERENCES**