Phoenix QT+ Cardiac Safety Evaluation Software

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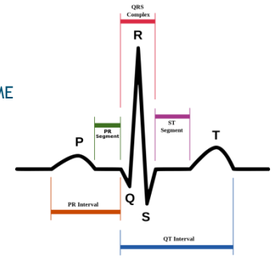
INTRODUCTION

- 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 pointes (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 AutoPilot 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



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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:

Goal is to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation

- Regulatory threshold is around 5 ms as evidenced by an upper bound of the 95% CI around the mean effect exceeding 10 ms

Randomized, blinded, positive- and placebo-controlled study in healthy subjects

- Investigational drug is given at therapeutic and supra-therapeutic doses

Results guide intensity of ECG monitoring during subsequent drug development

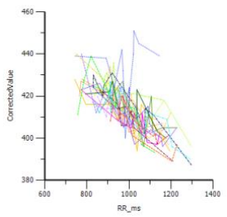
Phoenix QT+ is designed to easily perform analysis as specified in the ICH E14 Guidelines.

Phoenix QT+ Workflow

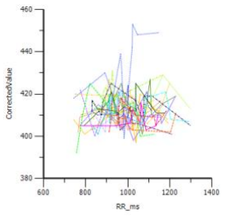
Heart Rate Correction:

(data from 400 mg Moxifloxacin)

Bazett: $QTcB = QT/RR^{0.5}$



Fridericia: $QTcF = QT/RR^{0.33}$



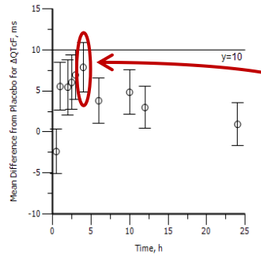
QT Transformation:

TAD, h	CP, ng/mL	QTcF, ms	Baseline QTCF, ms	ΔQTCF, ms	ΔΔQTCF, ms
0.5	0	401	402.66667	-1.6666667	-1.3333333
1	1.241	417	402.66667	14.333333	17.666667
2	1.68	409	402.66667	6.3333333	0.66666667
2.5	1.706	420	402.66667	17.333333	26.666667
3	1.409	406	402.66667	3.3333333	0.66666667
4	1.303	409	402.66667	6.3333333	8.6666667

QT+ Workflow Continued

Central Tendency Analysis:

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



Upper bound of this 95% CI exceeds 10 ms

Outlier Analysis:

Multiple limit values reported, due to lack of consensus

QT/QTc Interval	ΔQTc Interval	PR Interval	QRS Interval	Heart rate
>500 ms	>60 ms	>200 ms	>110 ms	>100 bpm
>480 ms	>30 ms	>125% baseline	>125% baseline	<50 bpm
>450 ms	≥ 30 & ≤ 60 ms			

Exploratory Plots:

Rsq = 0.09794, Intercept = 1.077, Slope = 1.349

Concentration - QTc Modeling:

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

Treatment	Dose	Cmax, ng/ml	Tmax, h	Median	Lower 5%	Upper 95%
Nudrug	20 mg	0.92	2.5	2.42	0.89	3.77
Nudrug	100 mg	4.86	2.5	7.5	5.35	9.11

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

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, 2005. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129357.pdf
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3. Garnett CE et al. "Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects." American Heart Journal, 2012 Jun;163(6):912-30.
4. Garnett CE et al. "Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review." Journal of Clinical Pharmacology, 2008; 48:13-18.