Data Quality in Small QTc Studies

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DISCLAIMER
Views and opinions presented are only my own
Data Quality in Small QTc Studies

The E14 Guidance on conducting thorough QT studies needs revisiting. Different replacement and/or modification concepts have been proposed. Most expect the QT/QTc investigations to be moved into the very early clinical tests, such as the SAD and MAD FIM studies.

This presentation is devoted to some aspects that should make the QT/QTc investigations as part of FIM studies practical and viable.
Data Quality in Small QTc Studies

- Electrocardiographic challenges of small clinical studies such as the first-in-man investigations
- Metrics of QTc data quality, power considerations of small studies
- Replacement and/or avoidance of standard positive control in small QTc studies and in conc-QTc analyses
- Approaches to PK/PD QTc modelling with the distinction of model types
- Reducing QTc variability in small studies
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Small clinical studies

• Data quality
Small clinical studies

- Automatic ECG measurement

Three ECGs taken in the same subject on the same day at 07:31:35, 07:32:44, and 07:34:40
Treatment bias in automatic measurement

QTcF in a quinolone study – courtesy of Dr Sarapa
Small clinical studies

- Drug-induced heart rate changes

![Diagram showing QT interval and RR interval with points labeled 'Predose' and 'Tmax']
Small clinical studies

- Drug-induced heart rate changes
Small clinical studies

• Drug-induced heart rate changes
Small clinical studies
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Power of small TQT studies

- Expected QTc difference between Rx and placebo [ms]
- Required number of subjects in a X-over study
- Standard deviation of QTc difference between placebo and period baseline [ms]

- 15 Comparisons
- 24 comparisons
- 40 comparisons

Time of the day [h]: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21

Standard deviation of QTc difference between placebo and period baseline [ms] vs. Time of the day [h]
Precision in QTc studies

• Metrics for comparison of data quality

Intra-subject standard deviation of QTc on placebo
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Assay sensitivity in QTc studies

Electrocardiogram II
Electrocardiogram V2

correlation coefficient of descending T waves 0.99860
difference 106 ms
Assay sensitivity in QTc studies
Assay sensitivity in QTc studies


ORIGINAL RESEARCH ARTICLE

Impact of Electrocardiographic Data Quality on Moxifloxacin Response in Thorough QT/QTc Studies

Lars Johannesen · Christine Garnett · Marek Malik
Assay sensitivity in QTc studies

• Reproducibility between subjects on placebo:
  Distribution of values
  \[(A_{t1} - B_{t1}) - (A_{t2} - B_{t2})\]
  where \(X_{t}\) is QTc measured in placebo subject \(X\) at time \(t\), for all pairs of placebo subjects \(A\) and \(B\) (\(A \neq B\)) and all pairs of time-points \(t1\) and \(t2\) (\(t1 \neq t2\)).
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PK/PD models
PK/PD models

Linear

Sigmoid $E_{\text{max}}$

$E_{\text{max}}$

Logarithmic
Electrocardiographic challenges of small clinical studies such as the first-in-man investigations

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Approaches to PK/PD QTc modelling with the distinction of model types

Reducing QTc variability in small studies
Reduction of QTc variability

Universal Correction for QT/RR Hysteresis

by

Marek Malik PhD, MD, a Lars Johannesen MSc, b,c
Katerina Hnatkova PhD, a Norman Stockbridge MD, PhD d

Submitted for publication on 6th February 2015
APD/HR hysteresis

QT/RR hysteresis
**QT/RR hysteresis**

- \( \overline{RR}_i = \vartheta RR_i + (1 - \vartheta) \overline{RR}_{i+1} \) \hspace{1cm} \text{interval based}

- \( \overline{RR}_n = RR_n \)

- \( 1 - e^{(-\lambda_I \frac{n}{L})} \) \hspace{1cm} \text{interval based}

- \( 1 - \frac{e^{-\lambda_I}}{1 - e^{-\lambda_I}} \) \hspace{1cm} \text{interval based}

- \( 1 - e^{(-\lambda_T \frac{\sum_{i=1}^{n} RR_i}{\sum_{i=1}^{L} RR_i})} \) \hspace{1cm} \text{time based}
QT/RR hysteresis

Contribution of individual RR intervals

History of QT reading [cardiac cycles]

Difference exponential - filter model

History of QT reading [cardiac cycles]
QT/RR hysteresis
QT/RR hysteresis
QT/RR hysteresis
QT/RR hysteresis
QT/RR hysteresis

Fridericia correction
QT/RR hysteresis
QT/RR hysteresis
QT/RR hysteresis
QT/RR hysteresis

• It is pointless to try to stabilize HR by supine positions

• Correcting the QT intervals to the hysteresis modeled RR’ leads to substantial reduction of the QTc variability

• Correcting QT interval for simultaneously measured RR interval or an average of small number of RR intervals should be avoided

• Study analysis windows may include variable HR episodes
• Preservation of the time course for hysteresis could serve the role of the positive control in TQTS, i.e., verification that the QT and RR data are adequate to detect clinically relevant repolarization effects of drugs where they exist.
Thank You