Recent insights from the FDA QT-IRT on concentration-QTc analysis and requirements for TQT study (‘waiver’) substitution

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Outline

- QT-IRT statistics
- Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)
  - Sample size
  - Exposure margin
- Common issues in submissions
- QT correction for heart rate effects
- Modeling analysis and reporting
- Forthcoming changes in data specifications
QT-IRT statistics for C-QT submissions under ICH E14 Q&A (R3)

- Dec 2015 - April 2018 (non-oncology products):
  - TQT substitutions (No moxifloxacin)
    - 14 favorable recommendations based on submitted data
    - 9 SAD studies, 4 SAD/MAD studies, 1 Other
    - 2 not recommended
  - Alternative TQT study (C-QT primary analysis- drug/moxifloxacin)
    - 1 completed study reviewed ('no effect' label)
    - 14 protocols agreeable; 3 recommended to change design; 2 recommended to change primary to central tendency analysis
  - Exposure margin (covering high clinical exposures, waiving positive control) is the predominant reason for not agreeing with the TQT substitution proposals
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)¹

- Study Design
- ECG Quality
- Dose range
- Sample size
- Assay Sensitivity
- C-QTc analysis

¹Refer to following publicly available slides (CSRC 2016):
General guidance for sample size

- **Sample size for Phase 1 type C-QT assessment**
  - **Subjects with placebo:** Plan for at least 8-10 evaluable subjects; can be pooled from different cohorts (e.g., 6:2 randomization to Trt:Placebo across 4-5 dose cohorts)

- **Sample size for alternative TQT (C-QT analysis for drug treatment and positive control)**
  - **Subjects with moxifloxacin:** Plan for at least 20-24 subjects (and equal number of placebo subjects for parallel study)²
  - **Subjects with drug treatment:** Plan using E-R simulations with expected effect size/variability etc.

²Huang D. *et al*, manuscript under review in *J Pharm Stat*
General guidance for assay sensitivity

Criteria for waiving requirement for positive control

• Evaluation of sufficiently high multiples (at least 2-fold) of highest clinically relevant exposure scenario*

*Highest exposure ($C_{\text{max}}$) at steady state due to intrinsic (e.g., organ impairment) or extrinsic factors (e.g., metabolic inhibition)
  - Based on normal dosing regimen (not the dosing regimen for sub-population); model based estimate can be acceptable

Example: A product with recommended dose of 20 mg BID in normal and 10 mg BID in severe renal impairment population. Highest clinically relevant exposure from QT-IRT’s perspective: Mean $C_{\text{max,ss}}$ with 20 mg BID (not 10 mg BID) dosing in severe renal impairment population.
General guidance for assay sensitivity

Criteria for waiving requirement for positive control

- Evaluation of sufficiently high multiples (at least 2-fold) of highest clinically relevant exposure scenario*
- Non-pharmacological approaches (e.g. bias evaluation\(^3,4\)) as an alternative to requirement for multiple fold exposure under consideration

\(^3\)Darpo B., CSRC-FDA workshop, 2016
\(^4\)Ferber G. et al, JCP, June 2016
Some common issues in submissions

• Expectation of exposure margin to waive the requirement of a positive control not achieved/unknown
  – Observed/estimated impact of organ impairment/DDI unknown
  – Not feasible to achieve requisite higher exposures (tolerability, pill-burden, saturable absorption etc.)
• Exposures for major metabolite(s) with long half-life not covered
• ECG sampling includes $T_{\text{max}}$ of parent drug but no sampling near $T_{\text{max}}$ of major metabolite
• In single dose trial, ECG sampling not for sufficient duration (at least 24 hours) to evaluate potential delayed effect
• Justification for pooling not adequate: e.g., Placebo absent in some studies
QT correction for heart rate effects

- The product is not likely to increase or decrease the heart rate significantly in the study
  - Use QTcF for the primary analysis
- The product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study
  - Consider alternative methods (e.g., QTcI), with wide enough span of heart rates at drug-free baseline visits to cover on treatment changes in heart rate within each individual
  - In cases where it may not be feasible to cover range of on-treatment large heart rate changes in off-treatment visits, consider engaging with the Agency to explore alternatives to bridge the information for adequate characterization of QTc/proarrhythmic effects

For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in “Scientific white paper on concentration-QTc modeling” (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and “Correction to: Scientific white paper on concentration-QTc modeling” (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).
Changes in Data Specifications

- Current state/issues: Dataset submissions in different formats (SDTM/ADaM, NONMEM, Other); Inconsistent coding of ADEG and ADPC pose challenge for C-QTc analysis datasets etc. → Difficulty for automated data quality checks, creation of standard analysis datasets etc.

ADEG: ECG data
ADPC: PK data
ADQT: Heart rate correction of QT
Summary

- Success in alleviating the need for TQT studies for multiple development programs based on C-QT analysis of data in early phase studies following ICH E14 Q&A (R3) implementation.

- Outlined general guidance for sample size and assay sensitivity aspects.

- Some challenges and potential solutions for design/analysis:
  - Bias evaluation as an alternative to requirement for multiple fold exposure margin (Dr. Johannesen)
  - Handling multiple moieties in a C-QT paradigm (Dr. Ferber)
  - Handling heart rate effects (Dr. Malik)