Assessment of QT Prolongation Risk Using Concentration Response Modeling – the Clinical Perspective-

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Outline

- Current status of ICH E14 in Japan
- Background of Revised Q&A about Concentration Response (CR) modeling
- Content of ICH E14 Q&A (R3)
- Implementation of CR modeling in Ph I studies to evaluate QTc prolongation risk in Japan
ICH E14/S7B Implementation

- **May 2005**  ICH E14 Step 4 signed off
- **Oct 2009**  ICH E14, E14 Q&A and S7B notification in Japan
- **Nov 2010 ~** the E14 guideline applied to new drugs seeking approval in Japan
- **Apr 2012**  ICH E14 additional Q&A (4 items) Step 4 signed off
- **Jul 2012**  additional Q&A notification in Japan
- **Mar 2014**  ICH E14 additional Q&A (4 items) Step 4 signed off
- **Jul 2015**  additional Q&A notification in Japan
- **Dec 2015**  Revised Q&A 5.1 on CR modeling Step 4 sign off
- **May 2017**  Revised Q&A 5.1 on CR modeling notification in Japan
Advantage of CR modeling in Ph I study

- Single ascending dose (SAD) and multiple ascending dose (MAD) studies: achieved plasma levels of the parent compound and abundant metabolites often substantially exceed therapeutic levels later observed in patients.
- All data across a wide range of plasma concentrations of the drug are used, and the power to detect and exclude small QT effects will therefore be substantially improved.

Ex: Result of CR modeling of Moxifloxacin
Use of CR modeling of QTc data

Concentration-response analysis, in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-time-point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug.

PMDA is going to accept QT assessment using CR modeling in Ph I studies.
When using a concentration-response analysis as the primary basis for decisions to classify the risk of a drug – the upper bound of the two-sided 90% confidence interval for the QTc effect of a drug treatment as estimated by exposure-response analysis should be $\leq 10$ ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed.
Point to consider when using CR modeling of QTc data (1)

- As much quality control as for a thorough QT study (TQT)
  - Standardized subject handling, robust ECG acquisition and measurement, timing of ECGs

- There are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure (large exposure margin) for drug and metabolites
  - Worst case scenario: The expected highest exposure due to intrinsic (e.g., hepatic, renal, age) and extrinsic (e.g., metabolic inhibition, food effects) factors

- Appropriate model (pre-specified)
  - Please refer to Dr. Ochiai’s presentation for details

- Assay sensitivity
CR modeling is NOT always suitable way to assess QT prolongation risk of the drug

- Drugs with substantial heart rate effects
- More than one molecular entity—multiple drugs or parent plus metabolites—contributes to the QTc effect
- Extended-release formulations with flat PK profile
- Drugs with PK/PD hysteresis
- Drugs that cause QT prolongation as a result of changes in protein synthesis or trafficking might demonstrate hysteresis.
- Non-hERG related changes in QT
Check points for regulatory submissions of CR modeling

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<td>highest clinically relevant exposure (Supratherapeutic)</td>
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<td>High multiples (at least 2-fold) of supratherapeutic</td>
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<td>Appropriate ΔΔQTc calculation</td>
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Points to be considered for use of CR modeling in Japanese NDA

D. Marathe, QTc Exposure-Response Modeling Workshop, 2016 (modified)

☆ Assessing **data adequacy** is important before CR modeling evaluation

**Study design**

- SAD/MAD: MAD is necessary if accumulation of the parent and/or relevant metabolites
- **Placebo control**: Control for potential bias introduced by study procedures and diurnal variations
- Baseline ECG
  - Pre-dose baseline (e.g. average of 3 time points over 1 hour)
  - Full day baseline to compute QTcI, if needed for drugs with heart rate effects
- Post-dose ECG/PK
  - Covers Tmax of parent/metabolite
  - Any delayed effects over 24 hours for single dose trial
  - 6-10 time points
Points to be considered for use of CR modeling in Japanese NDA

ECG quality

- Robust ECG acquisition and measurement:
  - Preferable to collect digital ECGs using the same model of calibrated ECG machine for each subject
  - Replicate (>3) recordings at each time point
  - Readers of ECGs blinded to time and treatment
  - All ECG’s in a single patient analyzed by the same reader
  - Same procedures for ECG analysis and reporting as in TQT

- Standardized Subject handling
  - Record ECG prior to blood draws, vital signs, or PD assessments
  - Timing and content of meals should be standardized
  - Supine, rest ≥10 min before ECG recording
  - The conditions of ECG recordings should be strictly matched for all dose cohorts
Sample size

- Subjects per treatment
  - 6-12 subjects per treatment cohort
- Treatment cohorts
  - Wide exposure range
  - At least 4 dose cohorts
- Subjects with placebo
  - At least 6 placebo controls; these can be pooled from different cohorts
Dose range

- Cover wide exposure range
- Therapeutic dose
- Highest clinically relevant exposure = Worst case scenario = the exposure obtained during metabolic inhibition and/or with renal or hepatic dysfunction
- Sufficiently high multiples of the highest clinically relevant exposure without a positive control for ECG assay sensitivity

☆ The \textbf{Cmax} of the highest dose in your QT assessment study must be at least >2 fold above Cmax in the worst case scenario
Exposure margin and dosing to satisfy requirement for waiving positive control

Assay Sensitivity

- Without a positive control, there is a risk of false negative result.
- E14 Q&A (R3): If there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure, a separate positive control would not be necessary.
- Exposure margin is drug dependent:
  - PK profile, variability in patients, non-clinical study results, risk profile of target patients
- Assay sensitivity is particularly important in the case of not large exposure margin.
- If a sufficiently high exposure has not been evaluated, a dedicated TQT that includes a positive control will still be needed.
- Validation will be needed for pharmacological or non-pharmacological approach for assay sensitivity.
Considerations for data pooling from multiple studies

- It is preferred that the concentration-response data come from a single study to minimize between-study variability.
  - Single study could be SAD/MAD under same protocol or conducted at same clinical site.
- If there is a need to pool data from multiple studies (e.g., to cover a wide range of dose/exposure or increase number of subjects exposed to drug),
  - Similar design and procedures (e.g. placebo, food)
  - Same robust clinical conduct and subject handling performed in each study
  - Similar ECG acquisition and ECG measurement methods across studies (at baseline and during the treatment)
Considerations for data pooling from multiple studies

- Pooling data from healthy volunteers and patients is generally not recommended
  - Patients taking concomitant medications or with comorbid conditions could influence the CR relationship
  - CR modeling using patient data is, however, valuable for drugs that prolong the QTc interval where the modeling objectives are to characterize the effect in patients and evaluate covariates that may increase a patient’s risk
Evaluation of QTc prolongation risk and proarrhythmic potential in Japanese NDA

Non Clinical
- In vitro/In vivo assays based on ICH S7b guideline

Ph I
- Robust, high-quality ECGs in SAD/MAD studies

Ph II
- Clinical doses
  - Drug-drug interaction, organ dysfunction etc → “worst case scenario”

Ph III
- Proper ECG monitoring
- Adverse events

CR modeling in Ph I appropriate?
- Yes
- No

Assessment using CR modeling

Thorough QT Or Additional assessment

Totality of evidence assessment of the risk of QT prolongation

NDA PMDA review
Points to be considered for use of CR modeling of foreign SAD/MAD study in Japanese NDA

☆ Basic idea of PMDA’s evaluation of QT prolongation risk using CR modeling is the same as when using foreign TQT data.

▶ Results of the CR modeling
▶ Comparison of PK/PD profiles between foreigners and Japanese
▶ Range of concentration used in CR modeling
  Therapeutic and supratherapeutic concentration
  Cover Japanese worst case scenario?
▶ Availability of Japanese ECG and safety information

☆ The purpose is an assessment of QT prolongation risk of the drug in the Japanese population by using CR modeling of appropriate data.
☆ Including Japanese data in CR modeling is not necessary. Results will however be interpreted in the context of Japanese patients.
Implementation of CR modeling in Ph I studies to evaluate QTc prolongation risk in Japan

- Recommend the use of consultation meeting when using CR modeling for decisions to classify the QTc prolongation risk of a drug.

- Recommend to refer to the upcoming technical White paper (with more details on methods and interpretation of CR relationship analysis):
  - By some pharmacometricians
  - Review by ICH E14/S7B discussion group
Thank you for your attention