Celerion’s Symposia Series: Bridging the Gap from Phase I to Proof-of-Concept

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Are You Ready for the Changing Cardiac Safety Regulations?

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Questions?

- Do I have to do a Thorough QT (TQT) study for my compound?
- If I have a TQT to conduct, what does that look like?
- If I don’t have a TQT to conduct, what does that look like?
- What approach to evaluating cardiac safety is the most cost effective for my compound?
- What approach does Celerion advocate for evaluating cardiac safety?
- Are ICHE14 and S7B changing?
- What other cardiac safety related regulatory changes are coming?
The Evolution of ICH E14

1997
- Health Canada Concept Paper

1999
- Joint Health Canada/FDA Concept Paper

2001
- FDA & CHMP Adopt E14

2003
- IRT Started

2005
- Points to Consider

2007
- Health Canada Adopts E14

2009
- E14 Q&A

2011
- ARITMO Project begins

2013
- preDiCT Project begins

2015

- E14 Q&A revised

- ??
Current Debate

- Does the TQT truly predict a compound’s proarrhythmia potential?
- There have been tremendous advancements in both pre-clinical and early clinical monitoring of arrhythmia potential since 2005. How does this:
  - Change proarrhythmia evaluation pre-clinically and/or clinically?
  - Change the need for a TQT?
- What has been the impact of ICH E14 and S7B on drug development? Is it worth the cost?
- What does a positive TQT really mean?
Cases of Torsades de Pointes

Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182
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Pre-clinical: CiPA

- Comprehensive In vitro Proarrhythmia Assay (CiPA) Initiative
  - Ion Channels
  - Stem Cell Myocytes
  - In Silico modeling

- Targeting S7B update in 2016
Early Clinical Cardiac Safety Evaluation

- Add intense ECG monitoring to early Single Ascending Dose (SAD) and Multi Ascending Dose (MAD) studies.
  - Pool data from different dose levels to evaluate concentration response relationship
  - Typically during SAD and MAD studies the highest doses are given allowing for better concentration response modeling
Early Clinical ECG monitoring

Early Clinical ECG monitoring

Early Clinical Cardiac Safety Testing

- Consortium for Innovation and Quality in Pharmaceutical Development/Cardiac Safety Research Consortium (IQ/CSRC)
  - Looking at five marketed drugs with a positive QT signal - one with a negative signal
    - Ondansetron, dofetilide, quinine, dolasetron, moxifloxacin
    - Levocetirizine
  - SAD-like study
- QT assessment criteria: The upper bound of the two-sided 90% confidence interval (CI) of the projected placebo-corrected delta QTcF is above 10 ms at the observed peak plasma level of the drug
- Positive control?
- Concern over potential false negatives (regulators) and false positives (sponsor)
Early Cardiac Safety Evaluation

- ECG data collection
  - Is data collection the same as a TQT?
  - Data acquisition and protocol requirements are very similar to TQT
- Time-points
  - Do we really need 10-12 time-points? Does this increase risk of false positive?
  - Typically response is seen around Tmax and 3-4 subsequent time-points
Early Cardiac Safety Evaluation

- What are the cost implications of adding extensive cardiac safety monitoring to SAD and MAD studies?
- If 6 dose levels analyzed estimated ~ $125k
  - Do all ECGs have to be analyzed?
  - Have the clinic assume 10-12 time-points but only analyze data from 5-6 time-points initially
  - If only top 3 doses are analyzed, additional ECG monitoring estimated ~ $95k
What does the TQT look like now?

Traditional Design

- Placebo
- Therapeutic Dose
- Supratherapeutic Dose
- Positive Control: Moxi

- ● Placebo
- ○ Study drug
- ■ Moxifloxacin dosing
- ◇ Intense ECG collection
What does the TQT look like now?

Crossover Design

Placebo
Supratherapeutic Dose
Positive Control: Moxi

- Placebo
- Study drug
- Moxifloxacin dosing
- Intense ECG collection
What does the TQT look like now?

Parallel with Nested Crossover Design

Moxi/PBO
PBO/Moxi
Therapeutic Dose
Supratherapeutic Dose

Day -1 1 2 3 4 5

N/2 N/2 N

- Placebo
○ Study drug
- Moxifloxacin dosing
- Intense ECG collection

DDM=average of Moxi/PBO and PBO/Moxi
Moxi/PBO=[QTcM(1)-QTcPB (5)]-[QTcPB(4)-QTcPB (-1)]
PBO/Moxi=[QTcM(5)-QTcPB (1)]-[QTcPB(-1)-QTcPB (4)]
Questions?