The sponsor's perspective: How can these data help us design phase 1 SAD/MAD studies to generate ECG data to replace the TQT study?

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Disclosure & Disclaimer

- I am employed by Astellas Pharma Global Development
- The opinions expressed in this presentation are mine, and not necessarily the opinions of Astellas.

Evolving industry practice for assessing risk of QTc prolongation

- ICH E14 & S7B were finalized in 2005.
- Preclinical, especially
  - hERG and
  - ECGs in dogs or other non-rodents
- TQT study

Optimal timing of the TQT study

- Ideally after phase 2a PoC study, for two reasons:
  - 75% of compounds fail in PoC
  - After PoC we have a better idea of the therapeutic and supra-therapeutic doses
- Ideally before phase 3, so that ECG monitoring in phase 3 can be based on a strong assessment of the risk or lack of risk of QTc prolongation as confirmed by the TQT study.

Sponsors do not want to wait until phase 2b to learn that their candidate has a serious liability

- ECG assessment in early phase 1
  - for Astellas initially in MAD studies with cohort size increased to 9 on active
  - More recently also in SAD studies
- Previously with less power than a TQT study
  - Goal to detect a 10 ms mean signal rather than a 5 ms mean signal

Exposure-Response Modeling

- Applying exposure-response modeling to early phase 1 data.
- References:
  - C. E. Garnett et al, Concentration-QT Relationships Play a Key Role in the Evaluation of Proarrhythmic Risk During Regulatory Review. J Clin Pharmacol 2008 48: 13-18
  - Hutmacher MM, Chapel S, Agin MA, JC, Lalonde RL. Performance Characteristics for Some Typical QT Study Designs Under the ICH E-14 Guidance. J Clin Pharmacol 48: 215-224, 2008
- Using exposure response we can match the power of the IUT test in a TQT study with standard cohort sizes of 6 on active at each dose.

What do the results of the prospective study presented at this workshop add?

- We should prospectively specify our approach to analyzing the QTc data in early phase 1.
- Even though hysteresis and non-linear exposure-response relationships are uncommon, we need to test for and deal with these complications
- The needed quality of the ECGs are the same as we are already doing

How do we change early Phase 1 SAD & MAD Studies?

- Include electronic ECGs read in a core lab for intervals.
- Ensure that subjects are not disturbed at the times that ECG extractions are planned.
- We do not need to add substantial additional burden to the early phase 1 SAD and MAD studies
  - Since the majority of compounds in early phase 1 fail at phase 2a PoC, we cannot afford much additional burden.

What baseline?

- No added value to a full day baseline, just do pre-dose baseline.
- Using the time-matched baseline for crossover studies increases variability, so that 50% increase in sample size is needed.
- Thus, eliminating the time-matched baseline is advantageous
- References
  - Abbott: Hosmane B & Locke C. A simulation study of power in thorough QT/QTc studies and a normal approximation for planning purposes. Drug Info J 39:447-455, 2005.
  - Lilly: Zhang L, Dmitrienko A, Luta G. Sample size calculations in thorough QT studies. J Biopharm Stat, 18: 468-482, 2008.
  - Merck: Bloomfield DM et al. The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. Clin Pharm Ther, 84: 475- 480, 2008.

Waive TQT study?

- The results of exposure-response analysis of early phase 1 data may justify a waiver of conducting a TQT study.
  - Depends on the attributes of your compound and the quality of your data.

When do we request a waiver, or plan a TQT study?

- After analysis of the ECG data in early phase 1 we can determine whether there is a significant slope to the concentration-QTcF relationship and estimate the QTcF for exposures within the range studied.
- We will not know the relevant therapeutic and supratherapeutic exposures until after phase 2a.
- So, phase 2b

Thank you for your attention.

Questions during the panel discussion

Please also feel free to ask me informally or E-mail:
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