PROSPECTIVE EARLY CLINICAL QT STUDY OF A TEST SET OF MARKETED DRUGS TO EVALUATE QT INTERVAL RESPONSE WITHOUT A TQT STUDY

CSRC Proposal by the QT Working Group of the IQ Consortium

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Background to IQ-QTWG proposal

- TQT study presents a large resource outlay
  - Plus additional 'knock-on' effects of conducting TQT prior to Phase 2 (C14, DDI, Special pop studies moved up).
- Could TQT be waived based on the Phase 1 QT data?
- The FDA analyzed >250 TQT studies in their database.
  - 55 were interpreted by the FDA as positive TQT studies.
  - Of these 55, 31 were performed after Jan 1, 2006.
  - Of these 31, the FDA has Phase 1 data for 17 drugs.
  - Of these 17, 6 drugs had a positive QT effect in Phase 1, as determined by the sponsor.
  - None of the early studies at the FDA had C-QT analysis.
- The FDA needs more Phase 1 QT data with modern design, conduct and analysis (post-January 2006).

IQ-QTWG proposal

- Conduct a prospective clinical Phase 1 study with marketed QT-prolonging drugs to evaluate if robust ECG monitoring with C-QT modeling could detect QT prolongation at the threshold of regulatory interest (10 ms).
- Determine if the Health Authorities would grant a ‘TQT study waiver’ based on the outcome of robust QT assessment with C-QT modeling in the end of the routine Phase 1 development.

Proposed study design

- Use a separate, identical crossover for every 3 drugs and placebo
- 8-12 healthy male adult subjects per crossover
  - It is a non-conservative design, as it doesn't mimic the full dataset from a SAD/MAD
  - To be justified by power calculation
- Each subject receives 2 single doses of the same drug in fixed sequence (low $\rightarrow$ MTD) on 2 consecutive days
- Each subject receives placebo
  - Pooled across treatment periods for analysis
- Blinding by 3rd party dosing
  - "Designated doser" who don't make other assessments
  - No identical match between placebo and active

Design Elements

- Test drugs
  - FDA will select marketed drugs with positive TQT from their data base
    - Number and properties TBD by the FDA
  - IQ-QTWG preferences to avoid the logistical challenges and cost of the proposed study:
    - Drug can be tested in healthy subjects
    - Single dose PK and QT is representative of the steady-state
    - Don’t include drugs with negative TQT result
- C-QT analysis concept
  - Obtain C-QT model-based estimate of the mean QT effect (θCmax) and the confidence limits around it.

Success Criteria

Successful test battery of clinically significant (LB>10msec?) positive compounds

- Criterion #1: Sensitivity reassurance
  - Never rule out an effect (Never conclude UB CI <10 msec)
  - A positive TQT outcome will be if the upper CI limit of the θCmax is >10 ms for either the therapeutic or supratherapeutic dose
  - A negative TQT outcome will be if the upper CI limit of the θCmax is <10 ms for both doses
- Criterion #2: Precision estimate (was it a good study?)
  - Ability to rule-in an effect – lower bound > 0msec (and upper bound >10msec?)
  - Slope estimates?
  - Width of CI? Within subject variability.

Implications for the TQT waiver

If the positive outcome of the proposed Phase 1 QTc study correctly predicts the positive TQT study outcome for all of the drugs selected by the FDA

then

A negative outcome of the future routine Phase 1 study conducted in the same robust fashion (e.g. SAD/MAD with C-QT) would support the TQT waiver.