QTcF postural changes as positive control for TQT studies: Eliminating the moxifloxacin group

William S. Wheeler, MD, FACC
Therapeutic Area Lead-Cardiovascular
Celerion
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Positive Control

- ICH E14 mandates a positive control to ensure assay sensitivity in a TQT study
- Most studies have used moxifloxacin, other compounds have been used but not generally adopted
- Moxifloxacin limitations
  - Administering a pharmaceutical compound
  - Blinding and overencapsulation difficulties
  - Greater than optimal effect
  - A separate arm or period required
Positive Control TQT-like Trial

- Randomized, double-blind, 2-period crossover comparing the QTcF effects of moxifloxacin 400 mg single dose po to placebo
- Detected typical moxifloxacin effect
- IRB approval
- 36 enrolled, 33 completed
- Study Baseline: 3 triplicate pre-dose ECG recordings
- Triplicate ECGs at 10 moxifloxacin vs. placebo time points (0.5, 1, 2, 2.5, 3, 3.5, 6, 7, 12, and 24 hours)
- Postural changes at -1, 1 and 3.5 hours immediately post ECG extractions for those time points (Traditional)
- Sit on side of bed for 10 minutes, stand for 7 (amended to 5) minutes and resumption of supine position for 7 minutes; ECG extractions last 2 minutes of each maneuver period
Postural Change in QTcF from TRADITIONAL at -1, 1 and 3.5 hours after dose.
Change QTcF vs. RR -1, 1 & 3.5

Change from Trad to Sitting

Change in QTcF (msec)

Change in RR (msec)

R Square = 0.004
Change in QTcF value = -8 + -0.005 * Change in RR

Change from Trad to Standing

Change in QTcF (msec)

Change in RR (msec)

R Square = 0.004
Change in QTcF value = -8 + -0.005 * Change in RR

Change from Trad to Supine

Change in QTcF (msec)

Change in RR (msec)

R Square = 0.033
Change in QTcF value = 2 + -0.012 * Change in RR
Conclusions

- In “real life” scenario, postural changes produced 5-7 ms change in QTcF
- QTcF change is more consistent with the intent of ICH E14 than moxifloxacin effect
- Single postural change replicate adequate for assay sensitivity while the second and third replicate confirmed that finding
- In view of the magnitude of the change and the variance, supine to sitting alone may be adequate and minimize possibility of AEs
- Further research to determine optimal number of postural change replicates seems warranted
Implications

• Because of the smaller QTcF change seen with postural changes than with moxifloxacin, study execution and ECG measurement precision are even more important when postural changes are used as the active control.

• Adoption of postural changes as the positive control in TQT studies would eliminate the need for a separate arm/period to determine assay sensitivity thereby resulting in much smaller studies at a significant cost savings.

• Potential for adoption of postural changes in SAD/MAD studies with PK/PD modeling.
Implications: Parallel Trial

Postural maneuvers are performed on all arms to maintain blind, but only analyzed in placebo.
Implications: Crossover Study

Period 1: Baseline ECG collection
Period 2: Moxifloxacin dosing
Period 3: Supratherapeutic
Period 4: Therapeutic

Groups 1, 2, 3, 4

Placebo, Moxifloxacin dosing, Supratherapeutic, Therapeutic, Postural/Placebo
Acknowledgements:

• Joy Olbertz, PharmD, PhD
• Sara Azzam, PhD
• Bruce DeGroot, PhD
• Katherine Clark
• Matt Wiedel, MS
• Questions