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

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Positive Control

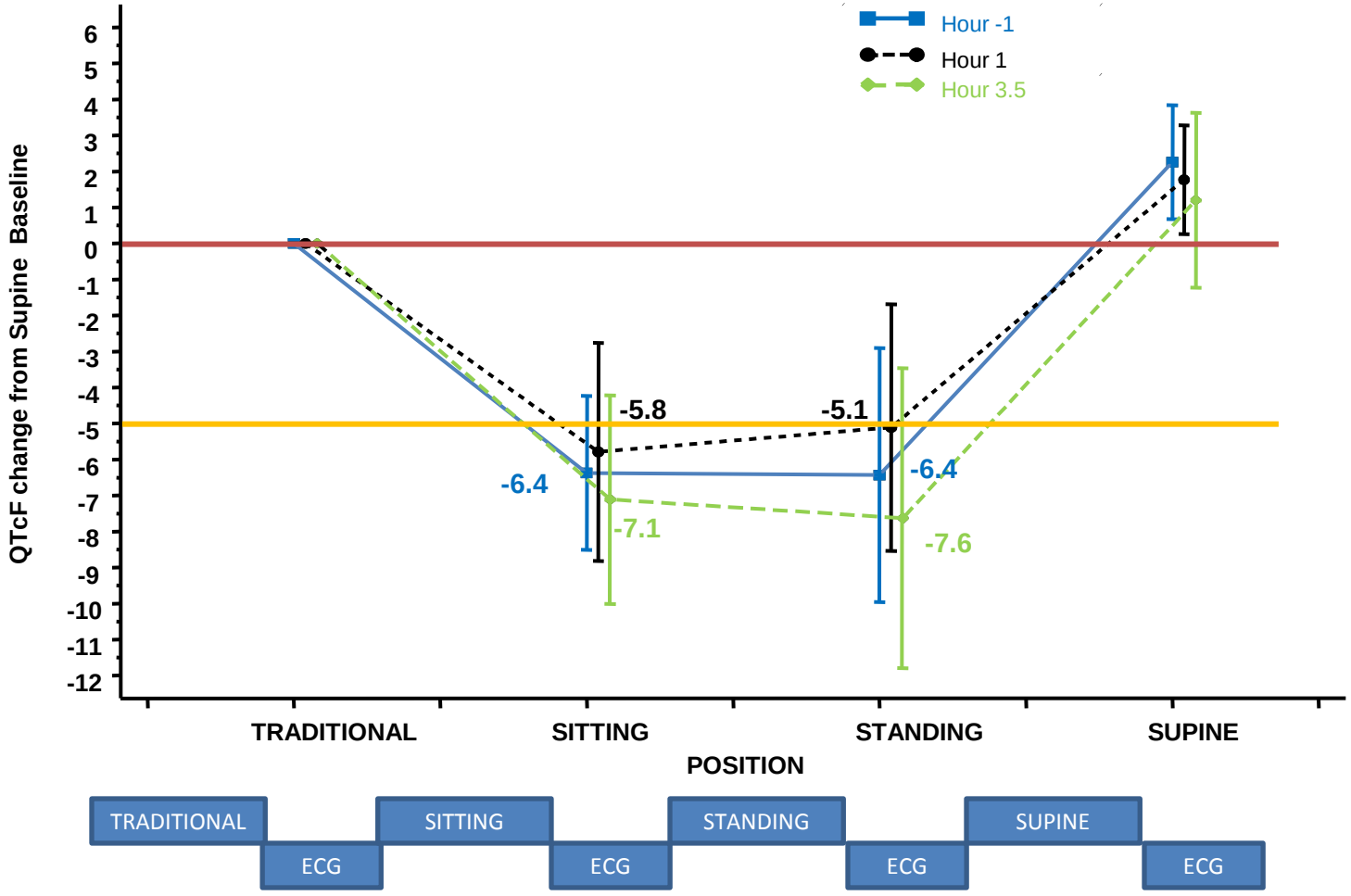
- ICH E14 mandates a positive control to ensure assay sensitivity in a TQT study
- Most studies have used moxifloxacin, other compounds have been used but not generally adopted
- Moxifloxacin limitations
  - Administrating a pharmaceutical compound
  - Blinding and overencapsulation difficulties
  -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

Positive Control TQT-like Trial

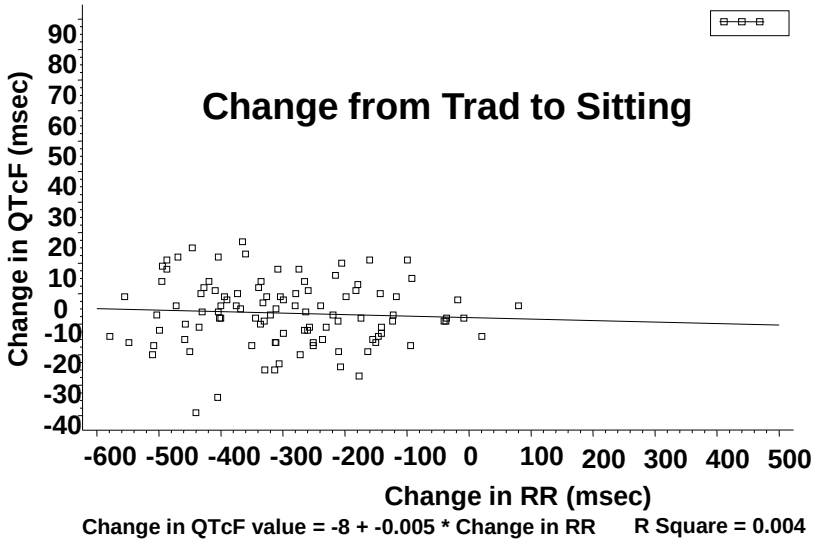
- Randomized, double-blind, 2-period crossover comparing the QTcF effects of moxifloxacin 400 mg single dose po to placebo
- Detected typical moxifloxacin effect
- IRB approval
- 36 enrolled, 33 completed
- Study Baseline: 3 triplicate pre-dose ECG recordings
- Triplicate ECGs at 10 moxifloxacin vs. 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

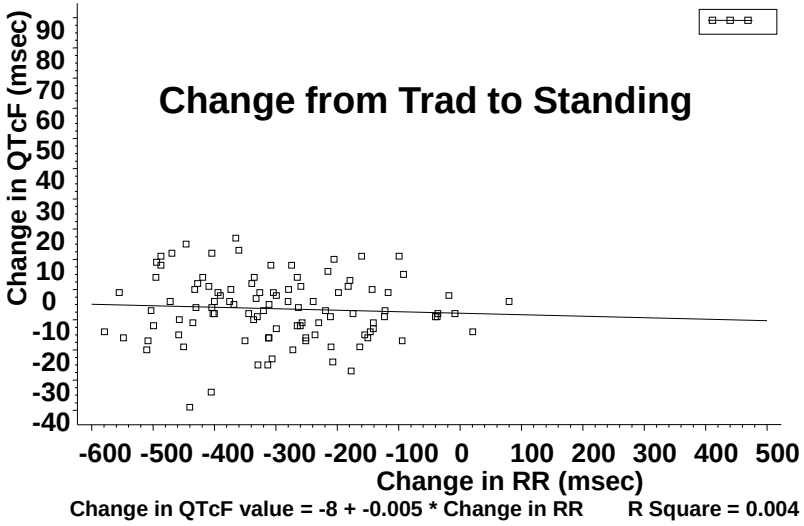
QTcF Postural Change Placebo Group

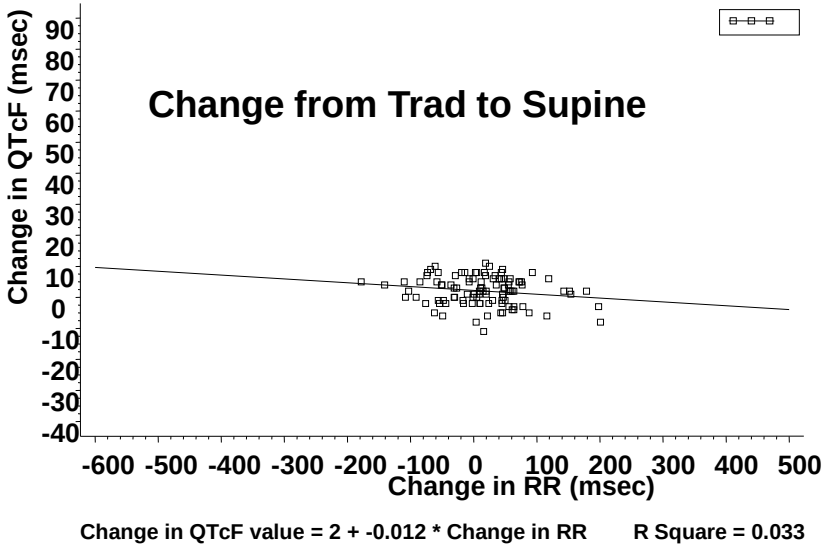
Postural Change in QTcF from TRADITIONAL at -1, 1 and 3.5 hours after dose



Change QTcF vs. RR -1,1 & 3.5







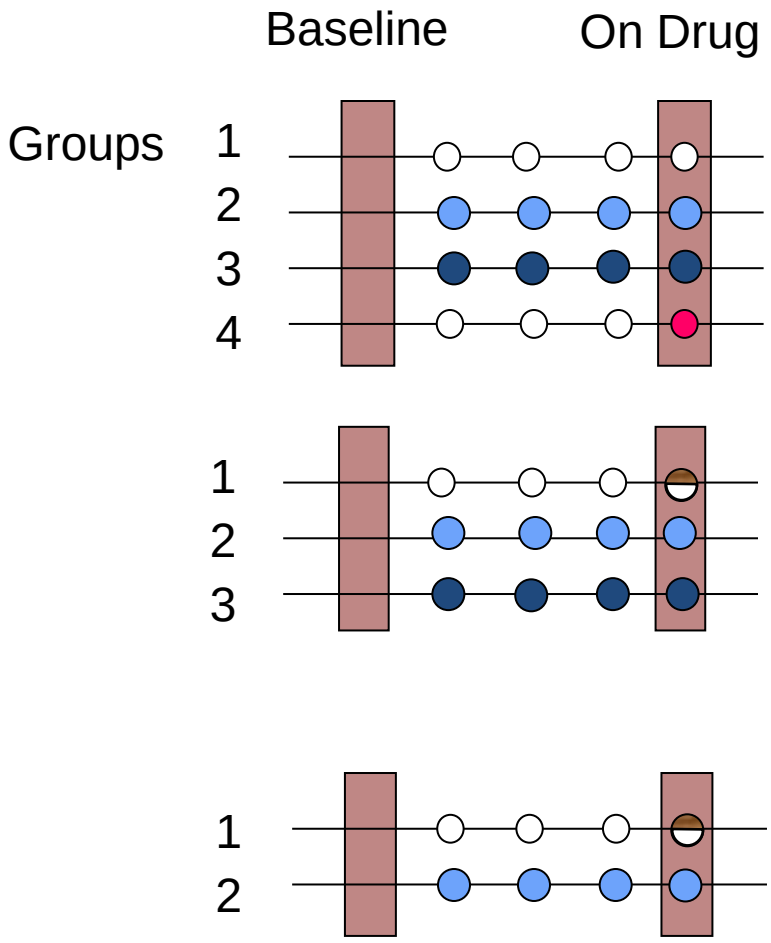
Conclusions

- 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



Moxifloxacin dosing

Placebo

Supratherapeutic

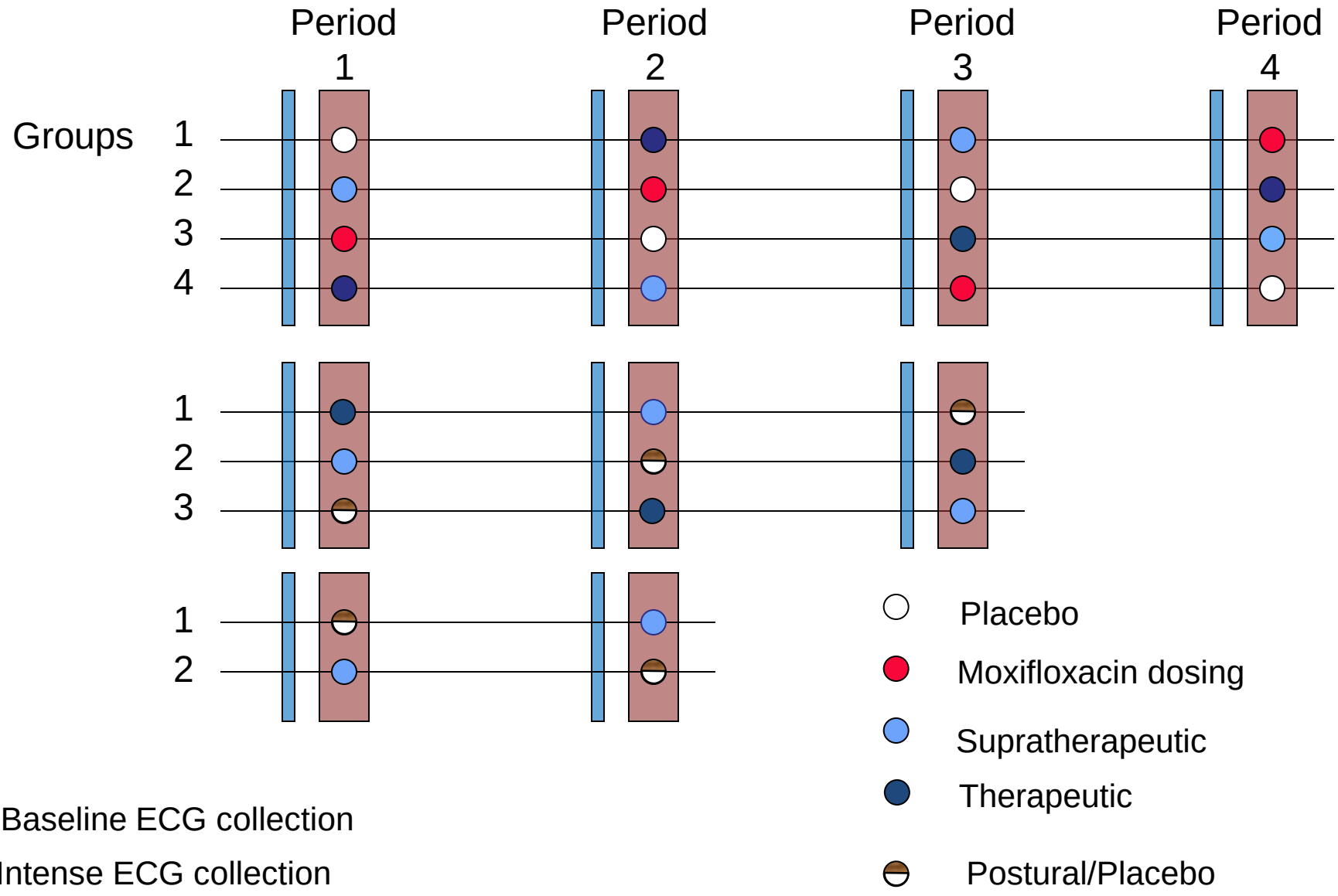
Therapeutic

Postural/Placebo

Intense ECG collection

Postural maneuvers are performed on all arms to maintain blind , but only analyzed in placebo

Implications: Crossover Study



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- Questions