Role of Concentration-Effect Modeling in Assessing Drug Effects on the QTc Interval from Early Phase I Data:

The Pfizer Experience

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Outline

- Rationale for concentration-effect (CE) modeling
- ECG Data Quality
- Standardized analysis plan
- Early Phase I vs TQT data
- Concluding Remarks

Rationale for CE Modeling

- Quantify drug related effects on QT interval
- Predict effects on the QT interval under alternate treatment conditions
- Accounts for variability in exposure
- Efficiencies gained through inclusion of all concentration and QT data across treatments
- Early phase clinical studies provide an opportunity to explore concentrations that are higher than those achieved following anticipated therapeutic doses

➢ **Opportunity to further utilize CE modeling to quantify drug effects on the QT interval and support risk assessment based on data collected during early phase clinical studies**

Phase I ECG Data

- At Pfizer, ECG quality standards are the same for both early Phase I and TQT studies
  - Collected by same staff at same research units
  - Use the same ECG machines
  - Adjudicated by the same clinicians
- Equivalent quality of QT data between early Phase I and TQT studies
- Is a positive control really required if companies have repeatedly demonstrated the ability to show an effect of moxifloxacin?

QTc analyses can be pre-specified

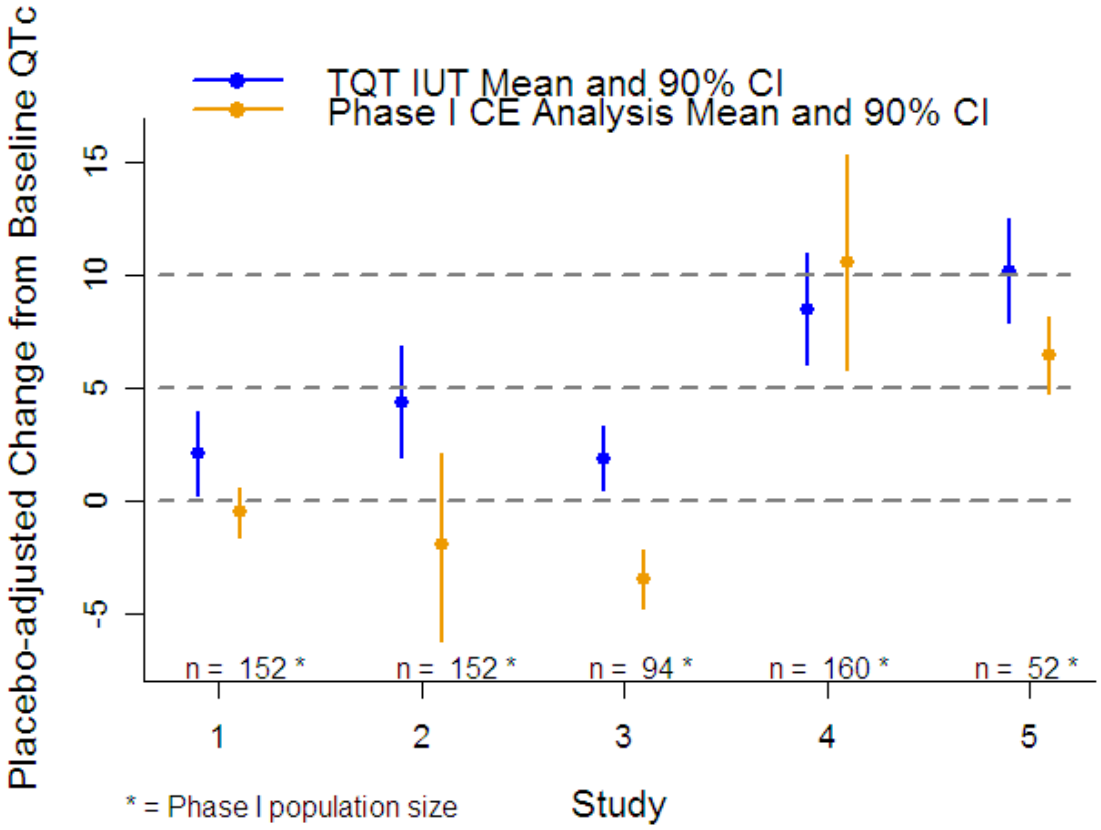
- Pfizer uses a standardized & pre-specified analysis procedure for analysis of QT data
  - Applied across the spectrum of QT analyses… from pooled analysis of Phase 1 data to TQT studies
  - Includes analysis methods, models, and reporting
- For TQT studies a specific analysis plan is completed before the study blind is broken
- For analysis of pooled data (e.g., SAD/MAD) where a report will be written, an analysis plan is written before the data are analyzed
  - Analysis follows the same standardized procedure

Early Phase I vs TQT Data

- Retrospective search for TQT studies conducted at Pfizer since ~ 2002
  - Identified 28 completed TQT studies
- Subsequent search for CE modeling results from Phase I data in those programs yielded only 5 examples
  - Potential reasons for lack of information:
    - Different practices at legacy companies
    - Only found slides with graphical assessments
    - No apparent signal so assume that no CE analysis was performed – graphical assessment only?
  - 2 additional Phase 1 datasets located but no CE analyses
  - 1-2 TQT studies currently planned with Phase 1 data available

Early Phase I vs TQT Results

- 3 Negative TQTs → consistent with Phase I CE results
- 2 Positive TQTs → CE point estimates > 5 msec



Concluding Remarks

- Equivalent quality ECG data can be collected from both early Phase I and TQT studies
- Evaluation of the need for a positive control is needed
- Pre-specified analysis plans are critical
- In this small sample:
  - Negative TQT studies were adequately predicted by Phase I data
  - Positive TQT studies had point estimates above 5 msec, but upper confidence limit excluded 10 msec in 1 example
    - Model misspecification? Time delay? Other reasons?

Concluding Remarks

- There is a currently a knowledge gap regarding the consistency with which CE analyses based upon early Phase I data can predict QT interval liability
- The onus is collectively upon us to explore this further and bridge the gap

Thank you for your attention!

Study 5 Results

- Model-predicted and observed QTcF