Regulatory decision-making for the assessment of ECG effects of new drugs: Exposure-response analyis

Kevin M. Krudys, Ph.D.
Team Leader
Division of Pharmacometrics
Office of Clinical Pharmacology

Disclosures

- The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

- The data presented is publicly available

Concentration-QT Analysis

- Drugs that prolong the QT interval have been shown to do so in a dose- or concentration-dependent manner

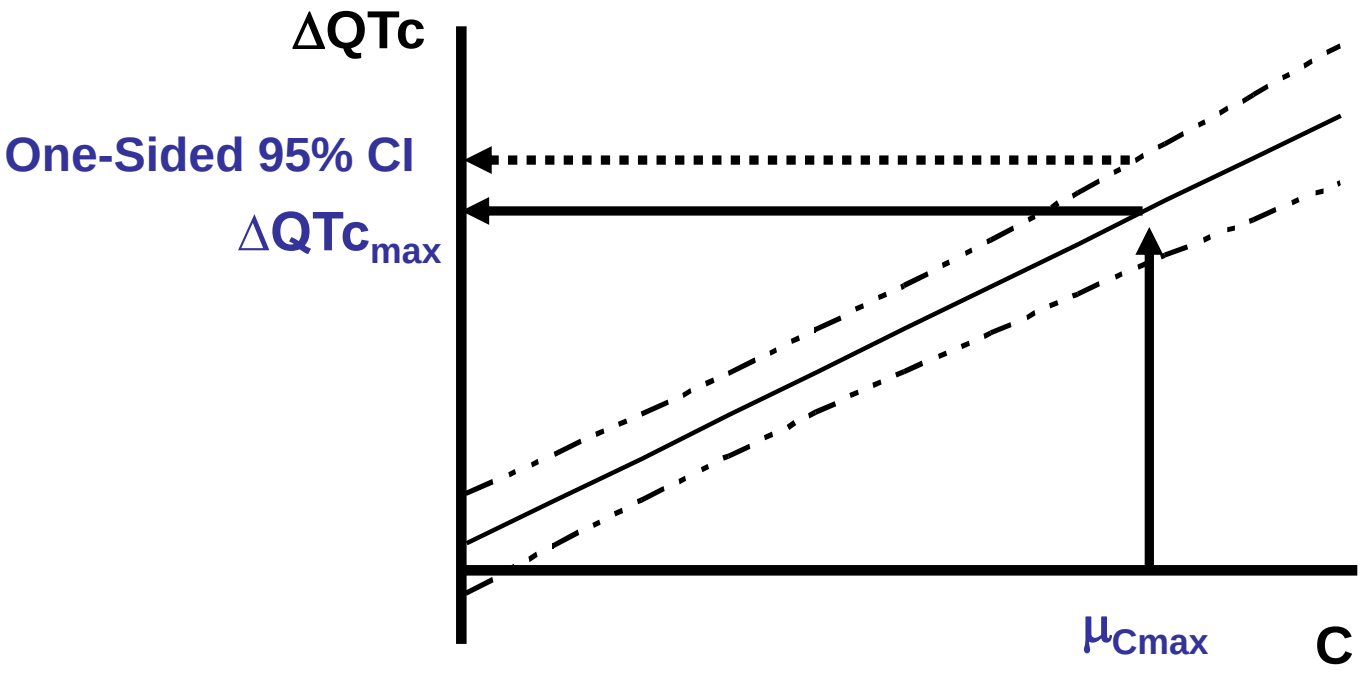
- ICH E14
  - C-QT analysis may provide additional insights to assist planning and interpretation of studies

- ICH E14 Q&A
  - C-QT analysis can be important component of a totality of evidence of the risk of QT prolongation
  - C-QT analysis applied to early clinical data seems promising in terms of enhancing confidence to characterize QTc prolongation

- "Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs*"

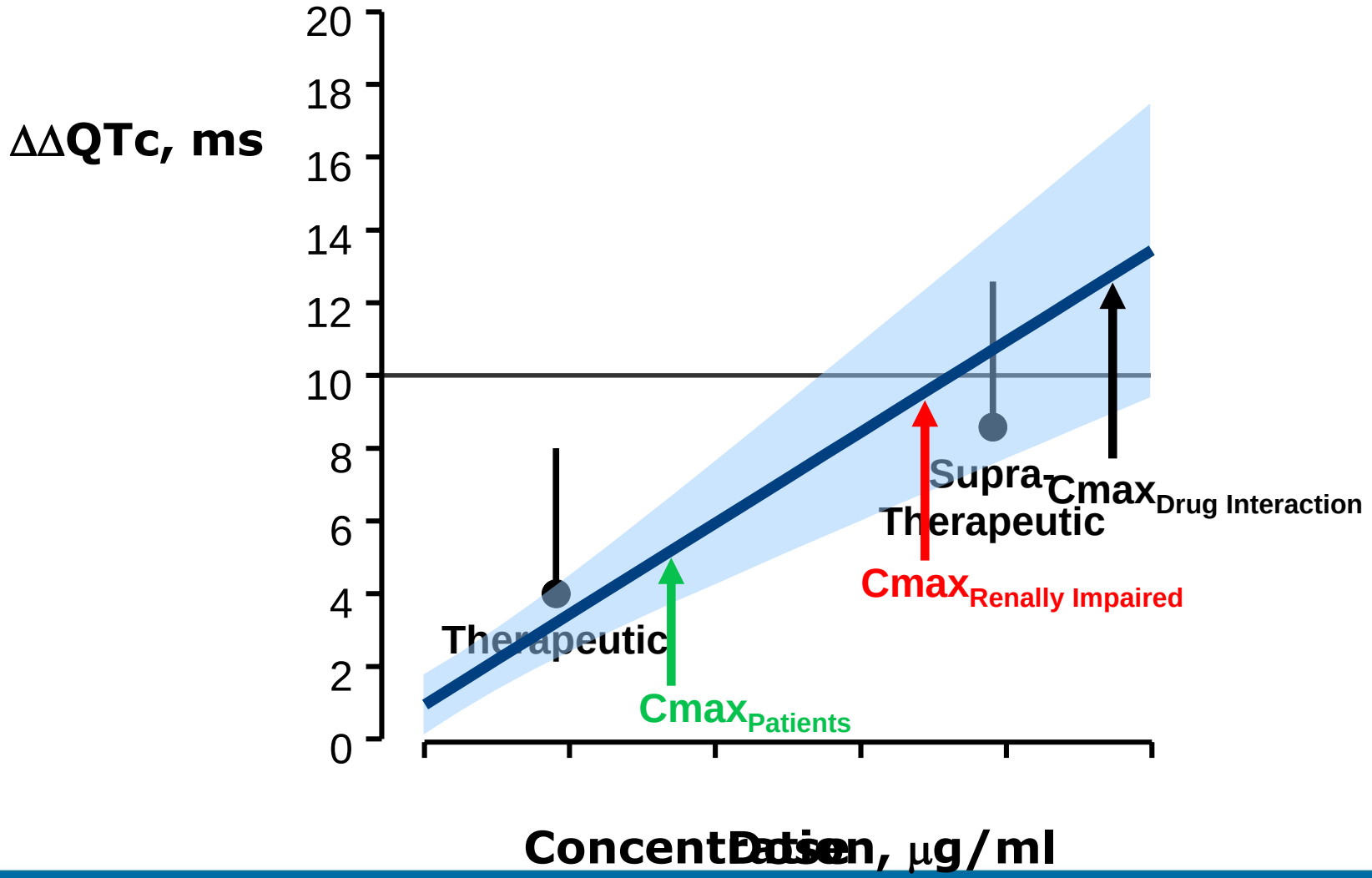
*Exposure Response Guidance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf
Dose Response Guidance. http://www.ich.org/LOB/media/MEDIA480.pdf

Mean ΔQTc at Exposure of Interest Is the Derived Endpoint from C-QTc Relationship

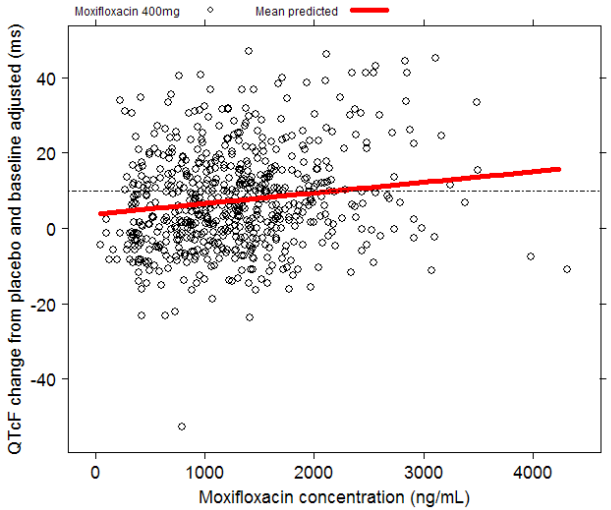


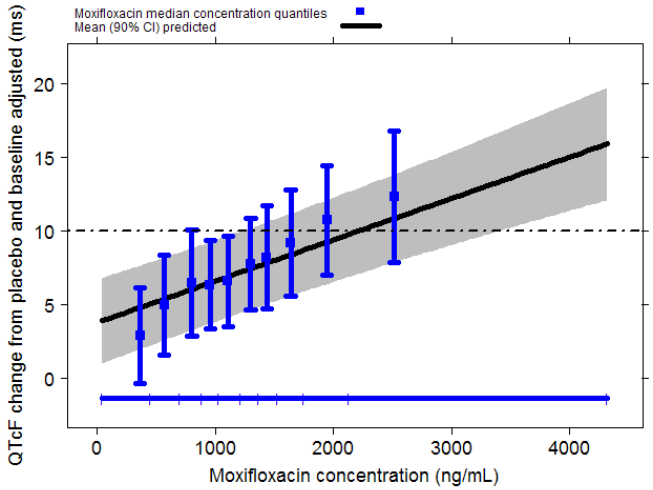
Important considerations include choice of structural model (linear, Emax) & investigation of hysteresis

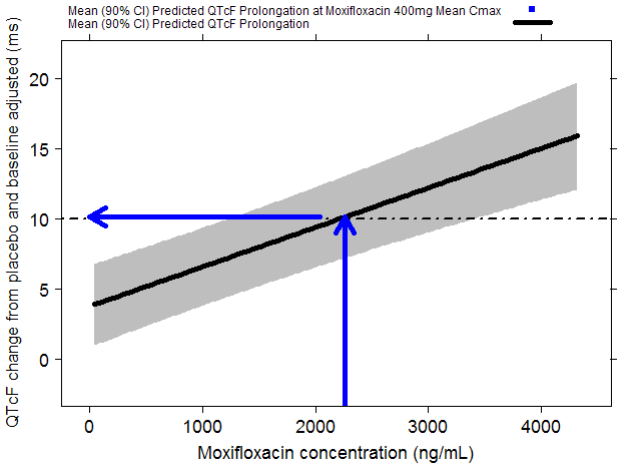
Concentration-QT relationship provides framework for regulatory decisions



C-QT Analysis is Routinely Performed by QT-IRT for All TQT Studies







Roles of Concentration-QT Analysis

- **Planning of a TQT Study**
  - Informing dose selection
  - Waive TQT study for drugs found to have positive C-QT relationship
- **Interpretation of TQT Study**
  - Clarify ambiguous results
  - Evaluate assay sensitivity of positive control
- **Quantify benefit-risk relationship**
  - Dose adjustments in special populations
  - Provide insights into regimens not directly studied
  - Effectively communicate risk

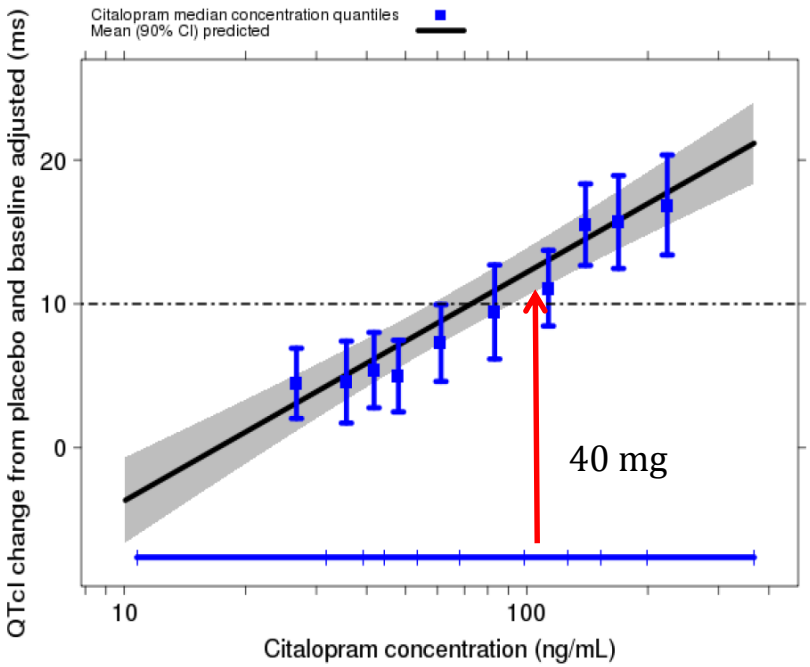
Case Study: Citalopram

- FDA received post-marketing reports of QT prolongation and torsades de pointes with citalopram
- TQT study was performed with doses of 20 mg and 60 mg

Treatment	Time (hour)	ΔΔQTcNi (ms)	90% CI (ms)
Citalopram 20 mg/d (on Day 9)	4	8.5	(6.2, 10.8)
Moxifloxacin 400 mg (on Day 9)	4	12.2	(9.9, 14.5)*
Citalopram 60 mg/d (on Day 22)	4	18.5	(16.0, 21.0)
Moxifloxacin 400 mg (on Day 22)	4	13.4	(10.9, 15.9)*
Citalopram 40 mg /d #	-	12.6	(10.9,14.3) #

Role of C-QT Analysis: Citalopram

- Effect at 40 mg dose was predicted using C-QT relationship
- Doses > 40 mg/day are not recommended
- Dose capped at 20 mg for poor metabolizers or concomitant CYP2C19 inhibition (1.4 to 1.7-fold increase in exposure)



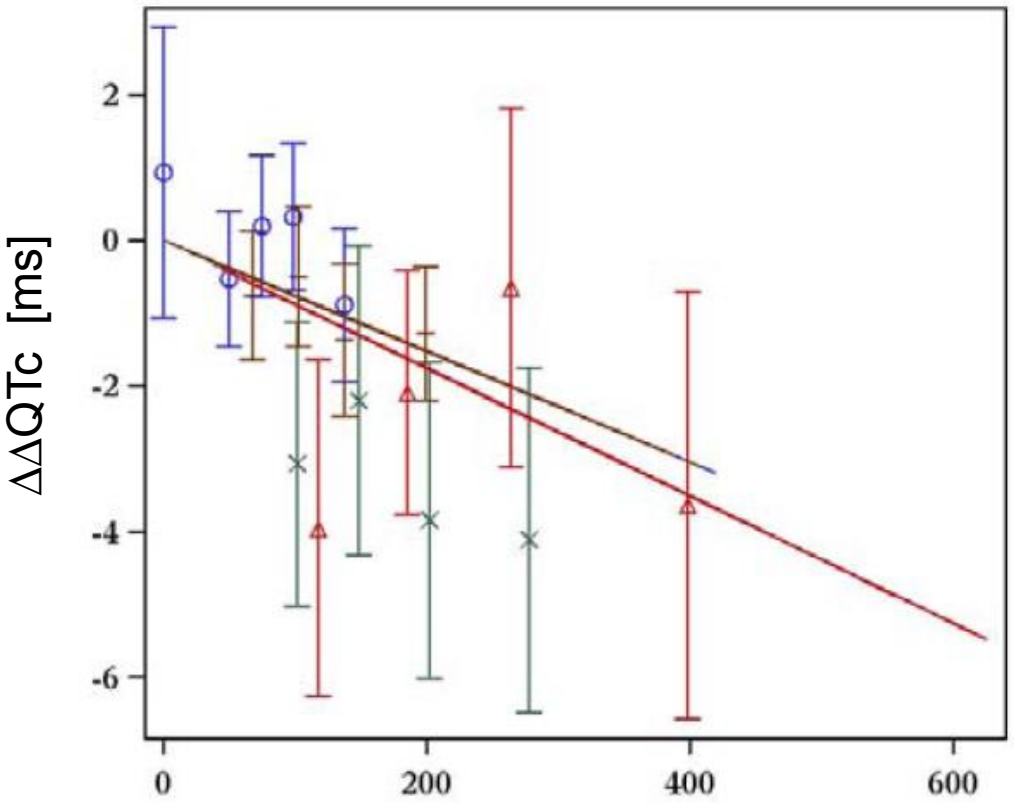
*Similar analysis was performed for escitalopram

Exposure-Response Analysis Using "Non-TQT" Data

- Expectations in a "Non-TQT" setting
  - Quality ECGs (replicate, centrally read)
  - Reliable baseline data
  - Time-matched ECG/PK collection
  - Range of doses/exposure

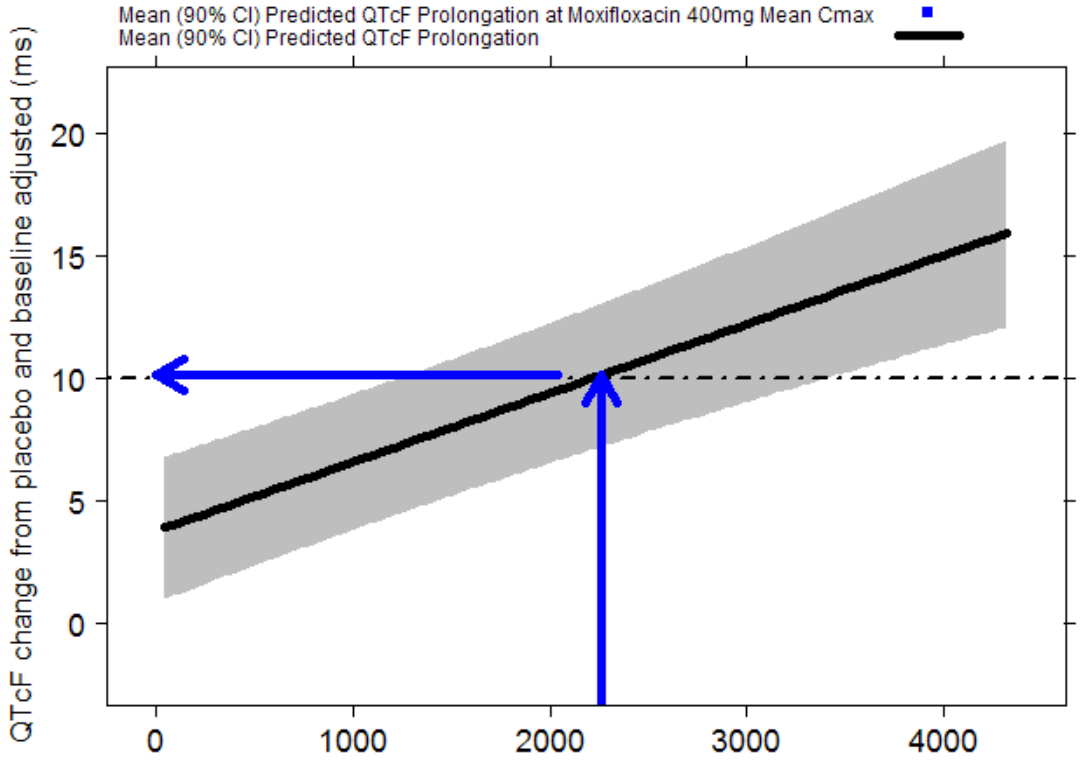
- Types of Studies
  - Early clinical studies (SAD, MAD)
  - Dose finding
  - Pivotal trials
  - TQT substitute studies (i.e., oncology)

Example 1: Consistent Negative Concentration-QT Observed in Early Clinical Studies



- ✓ No apparent QT prolongation effect has been identified
- ✓ No need for further dedicated / thorough QT studies

Example 2: Positive Concentration-QT Observed in SAD Study



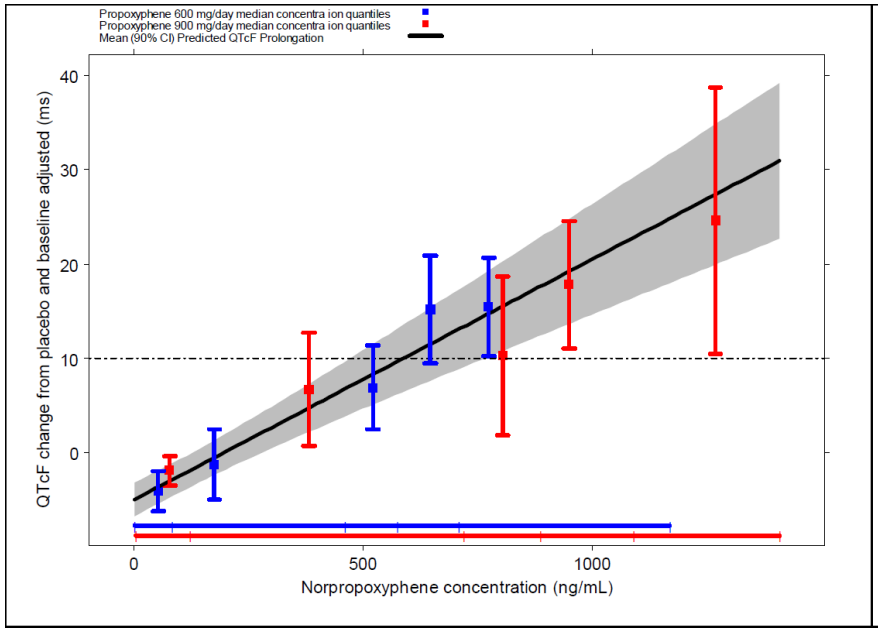
- ✓ Planned therapeutic Cmax << Cmax at which ΔΔQTc = 10 ms
- ✓ No need for TQT studies (not a prolonger)

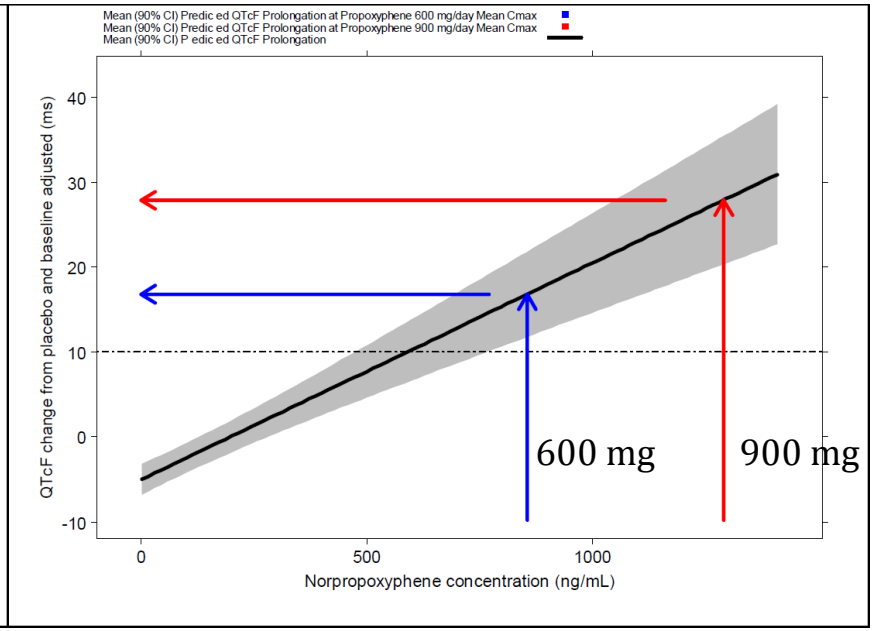
Example 3: Propoxyphene

- Post-marketing requirement to conduct a MAD study to establish the maximum tolerated dose to be used in a TQT study
- MAD study design
  - Cohorts
    - Dose 1: 600 mg (6 active, 2 placebo)
    - Dose 1R: 600 mg (6 active, 2 placebo)
    - Dose 2: 900 mg (6 active, 2 placebo)
  - Time-matched baseline ECGs on Day -1
  - Triplicate 12-lead ECGs

Example 3: Propoxyphene (Results)

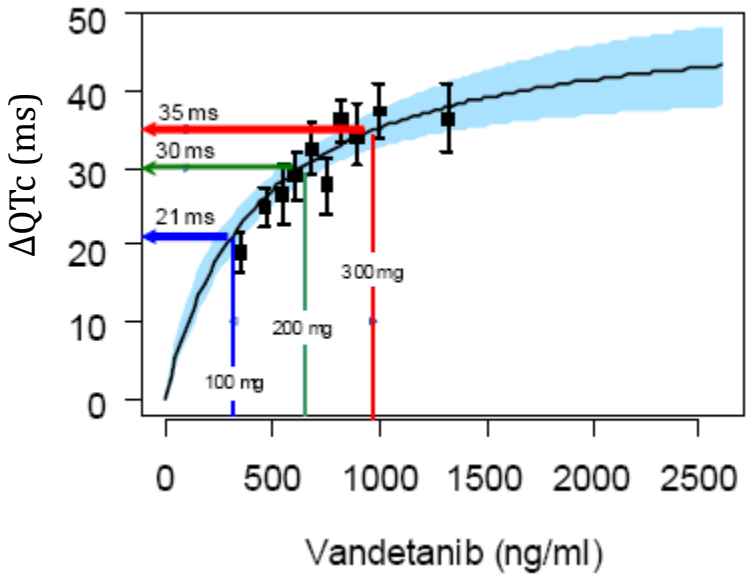
- Clear C-QT relationship established for norpropoxyphene
- Relationship was used to predict QTc prolongation for different subpopulations
- TQT study was not conducted
- Propoxyphene was withdrawn due to risk of cardiac toxicity



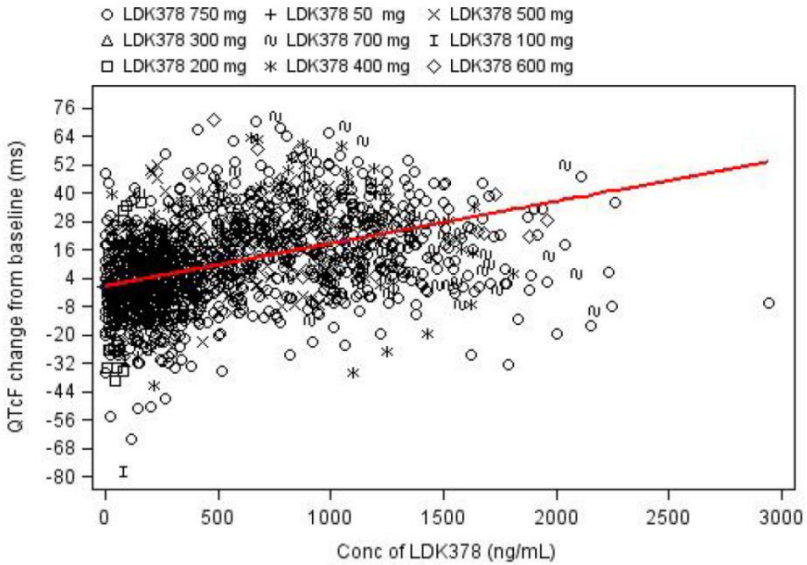


Example 4: Oncology

- Vandetanib
  - Data from patients in phase 3 clinical trial



- Ceritinib
  - Data from patients in dose-escalation study



✓C-QT relationship provided support for labeling, risk/benefit assessment and PMRs for investigation of lower doses

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000ClinPharmR.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf

Key Points

- Exposure-response analysis:

1. Is a key analysis routinely performed for all new drugs

2. Provides the framework from which QT-related regulatory decisions are made

3. Is already being applied to early phase or non-TQT data to support regulatory decisions