Experience Regarding Expectations and General Guidance for Regulatory Submissions under ICH E14 Q&A (R3) for TQT Study Substitution Requests Based on Concentration-QTc Analysis

Dhananjay Marathe

ACCP
American College of Clinical Pharmacology®
Advancing Clinical Care through Pharmacology®

2020 ACCP Annual Meeting
Translating Clinical Pharmacology Research into Patient-centered Care

Outline

- Relevant regulatory guidances
- Various modalities/attributes - QTc characterization requirement
- General guidance for TQT substitution using C-QTc analysis of early phase data
- Non-pharmacological and in vitro data as an aid
- Concentration-response analysis using novel ECG biomarkers
- Pointers for analyzing/presenting conc-QTc data
- Contents of QTc submission package for regulatory agency (FDA)

Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT)

- Provides expert review advice to sponsors and new drug review divisions
- Monitors the FDA ECG Warehouse
- Contributes to evolution of science through working groups, consortiums, collaborative projects and inter-agency exchange of ideas
- Undertakes development of databases, templates and tools to facilitate review and research activities

Regulatory Requirements: ICH E14 (2005) and S7B

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Guidance for Industry

S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Study	Assay Sensitivity	Analysis
• TQT (A randomized, placebo- and positive-controlled study with thera. and suprathera. drug doses)	• Moxifloxacin	• IUT (*primary*) • C-QTc (*supportive*)

Ref: Marathe D., *ASA meeting*, 2017

QTc characterization regulatory requirements

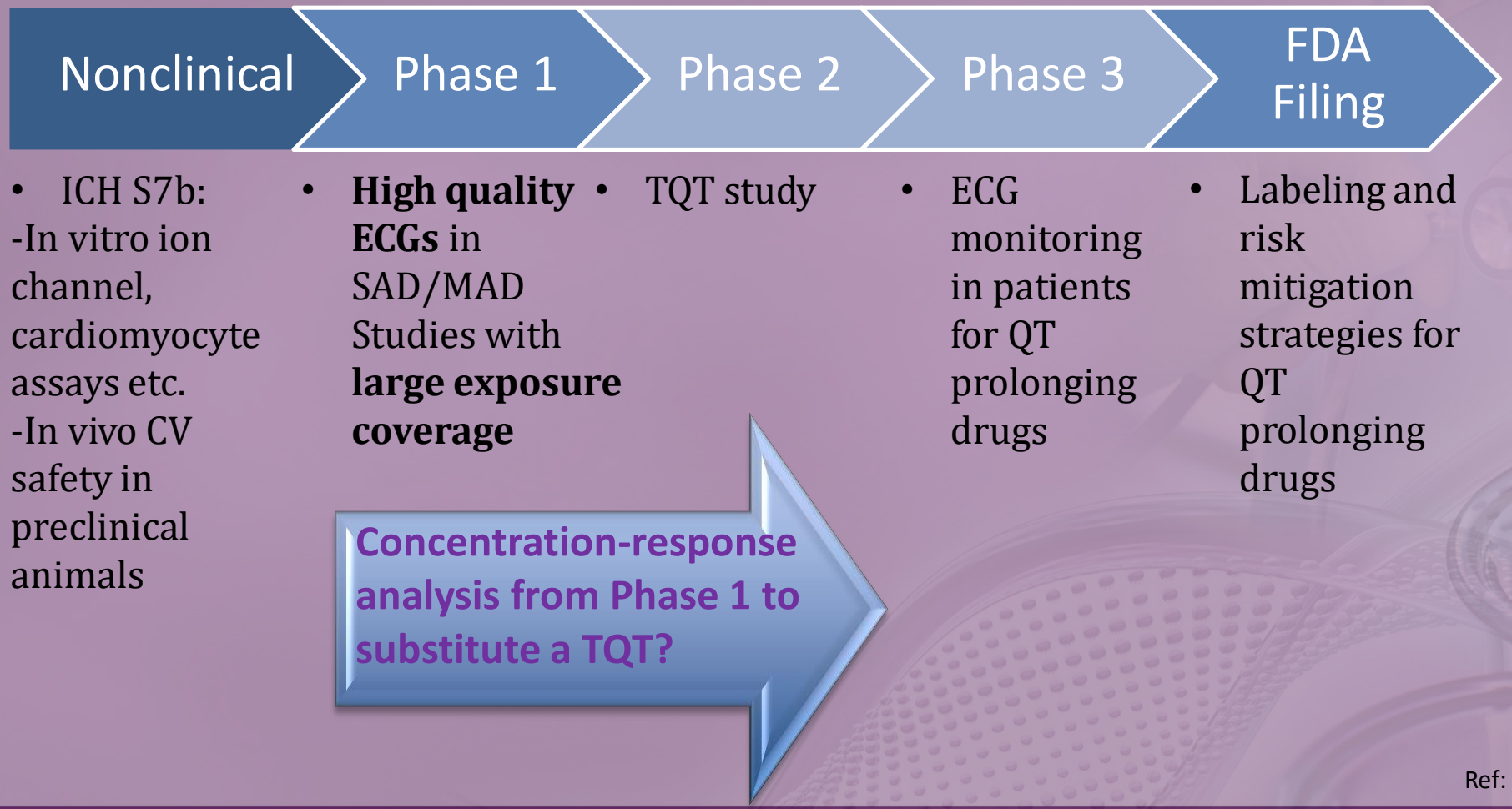
Modality	Requirement	Comment
Any indication		
Large proteins / mAb	No	• Unlikely to have direct ion channel interaction; Refer E14 Q&A (R3)*, 6.3
Non-Onc indication *(Exclude small QTc effects [10 ms], using TQT/TQT-substitution)*		
Small molecules	Yes	• E14 not applicable for locally acting drugs (sub-nanomolar systemic conc.) • Intermediates, currently as small molecules; no specific regulatory guidelines; engage with regulators for alternatives
ADCs**	Yes for small drug	
Intermediates (Oligos, siRNA, small peptides)	Yes	
Onc indication *(Exclude large QTc effects [20 ms], e.g. using QT sub-study in patients)*		
Above 3 modalities	Yes (same as above)	• E14 Q&A (R3), 6.1: Without a +ve control…if upper 90% CI <10 ms…unlikely to have 20 ms effect • Different labeling implications for < or > 10 ms effect and C-QT relationship

Onc = Oncology/oncology-like based on benefit-risk;

ADCs = Antibody-drug conjugates

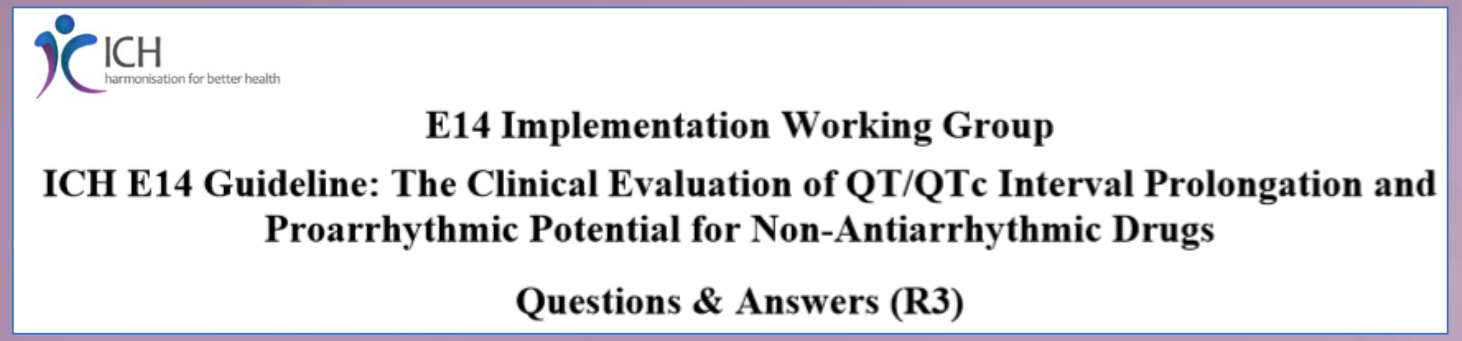
Ref: *ICH E14 Q&A (R3); **Liu R et al, *Expert Opinion on Biological Therapy*, 2016, 16:5, 591-593

QTc evaluation in drug development



Ref: Garnett C., *CPAC*, 2017

Regulatory Requirements: ICH E14 Q&A (R3) (2015)



Study	Assay Sensitivity	Analysis
• TQT	• Moxifloxacin	• IUT (*primary*)
		• C-QTc (*supportive*)
• TQT Substitution (SAD/MAD)	• Exposure margin to waive +ve control	• C-QTc (*primary*)
• Alternative TQT	• Moxifloxacin	• C-QTc (*primary*)

Ref: Marathe D., *ASA meeting*, 2017

A number of submissions to FDA with C-QTc as the primary analysis under R3 (Dec 2015 - April 2018; non-oncology products)

TQT Substitution (no Moxi)	Alternative TQT (with Moxi)

• 14 favorable cases
  – 9 SAD
  – 4 SAD/MAD
	• 1 favorable case
	• 14 protocol agreements
	• 5 protocols recommended to change design or primary analysis

- Several submissions (>30) did not qualify as TQT substitution, predominant reason being a lack of adequate exposure margin

Ref: Marathe D., CSRC, 2018

General guidance: TQT Substitution based on C-QT

Study Design	❑ SAD/MAD ❑ Placebo control ❑ Baseline ECG ❑ Post-dose ECG/PK
ECG Quality	❑ Data acquisition ❑ Design/Trial Conduct ❑ Data pooling considerations
Dose Range	❑ Wide exposure range ❑ Therapeutic dose ❑ highest clinically relevant exposure (*Supratherapeutic*) ❑ High multiples (at least 2-fold) of *supratherapeutic*
Sample size	❑ Subjects per treatment ❑ Treatment cohorts ❑ Subjects with placebo
Assay Sensitivity (positive control)	❑ Meets criteria for waiving requirement
C-QTc Analysis	❑ Pre-specified analysis plan ❑ Exploratory plots ❑ LME model (or alternative) ❑ Goodness of fit ❑ Appropriate ΔΔQTc calculation

J Pharmacokinet Pharmacodyn. 2018 Jun;45(3):383-397. doi: 10.1007/s10928-017-9558-5. Epub 2017 Dec 5.

Scientific white paper on concentration-QTc modeling.

Garnett C[1], Bonate PL[2], Dang Q[3], Ferber G[4], Huang D[3], Liu J[5], Mehrotra D[6], Riley S[7], Sager P[8], Tornoe C[9], Wang Y[5].

Ref: Marathe D., *CSRC*, 2018;
Marathe D., *CSRC*, 2016;
Garnett C. et al, *JPKPD*, 2018

General guidance: Sample size

❖**Sample size for Phase 1 type C-QT assessment**

- **Subjects with placebo:** Plan for at least 8-10 evaluable subjects; can be pooled from different cohorts (e.g., 6:2 randomization to Trt:Placebo across 4-5 dose cohorts)

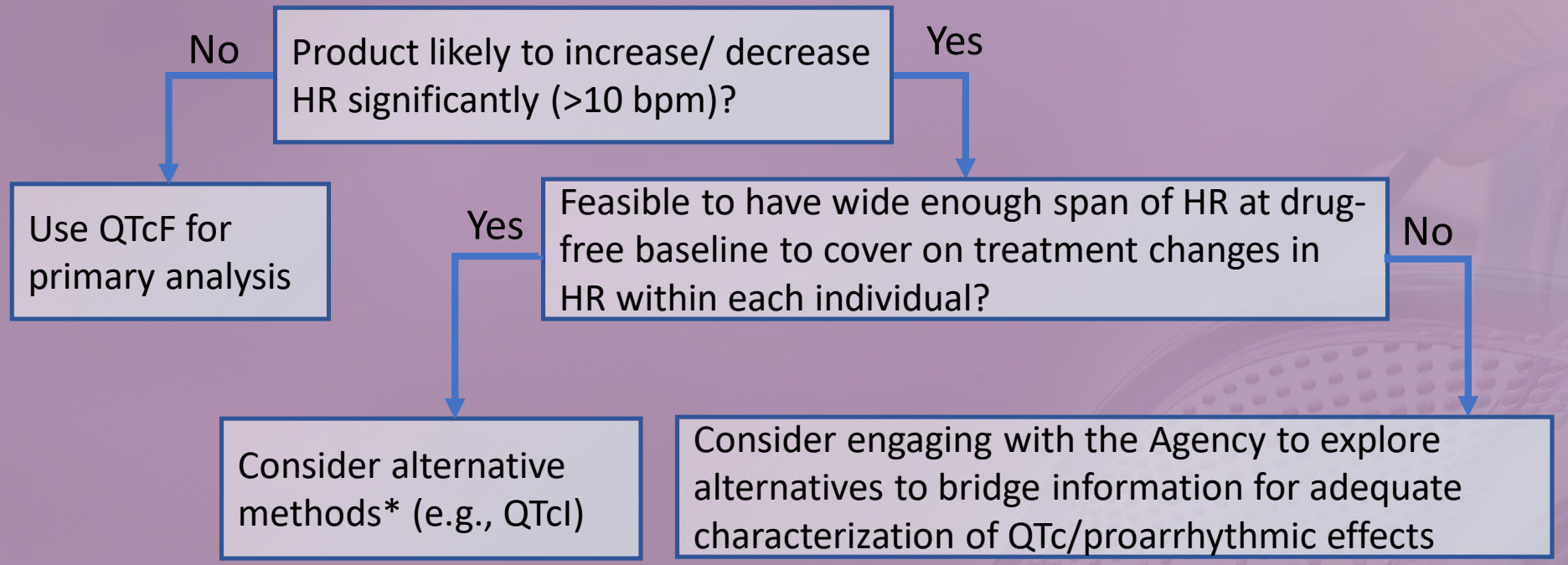
❖**Sample size for alternative TQT (C-QT analysis for drug treatment and positive control)**

- **Subjects with moxifloxacin:** Plan for at least 20-24 subjects (and equal number of placebo subjects for parallel study)*
- **Subjects with drug treatment:** Plan using E-R simulations with expected effect size/variability etc.

Ref: Marathe D., CSRC, 2018;
Huang D. *et al*, J Biopharm Stat, 2018

General guidance: Handling QT correction for heart rate (HR) effects

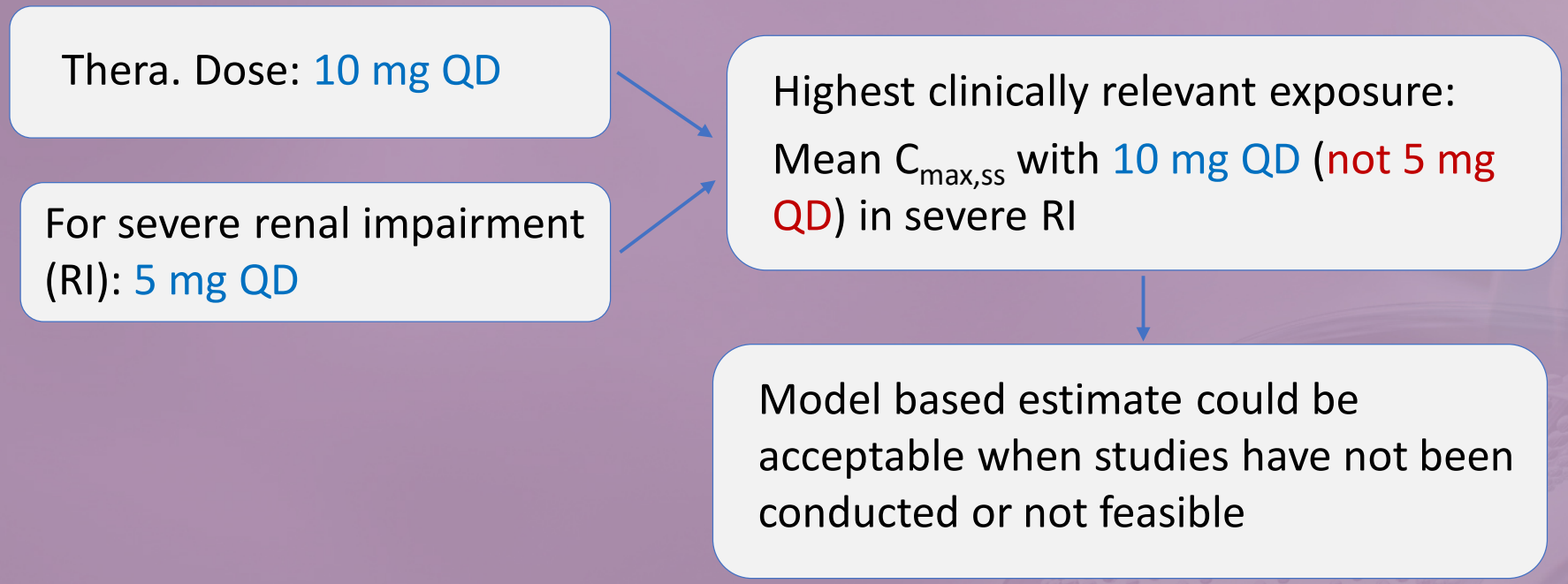
- Previously, as suggested by Tornoe et al (2011), sponsors assessed the best choice of QTc correction method based on on-treatment data.
- Recent change in thinking at IRT with more insight that the on-treatment data could be highly confounded for such decision.



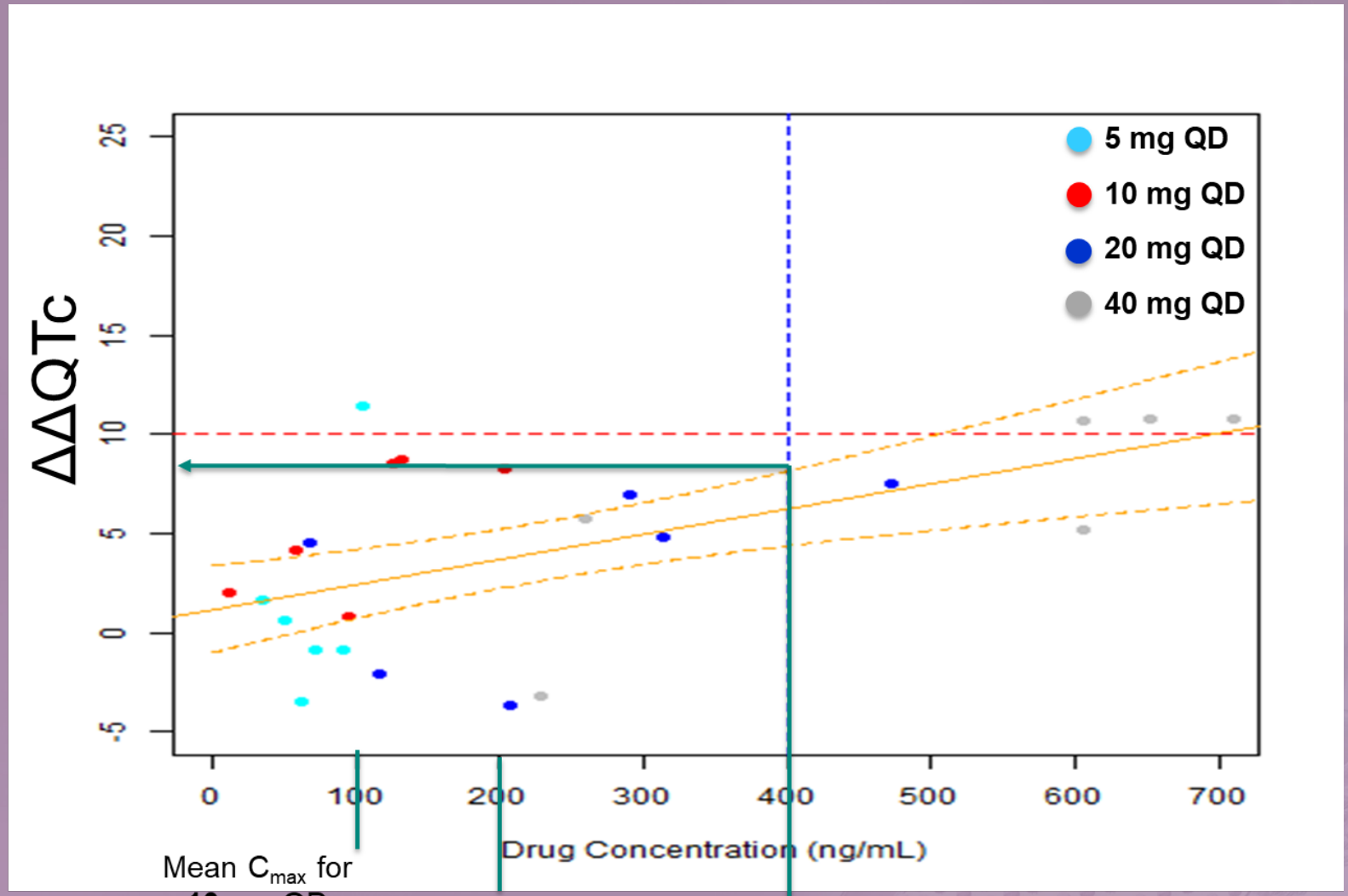
Ref: Marathe D., *CSRC*, 2018;
*Garnett C. et al, *Am Heart J*, 2012

General guidance: Waiving requirement of positive control for assay sensitivity

- Evaluation of at least 2-fold of highest clinically relevant exposure (due to intrinsic or extrinsic factors, e.g., organ impairment, metabolic inhibition etc.)



Ref: Marathe D., *CSRC*, 2018



Mean C_{max} for **10 mg** QD

C_{max} for Severe RI with 10 mg QD **~20 mg** QD in healthy

2-fold exposure margin **~40 mg** QD in healthy

Ref: Marathe D., CSRC, 2016

Non-pharmacological approaches (e.g. bias evaluation) as an alternative when desired exposure margin not achieved….achievable

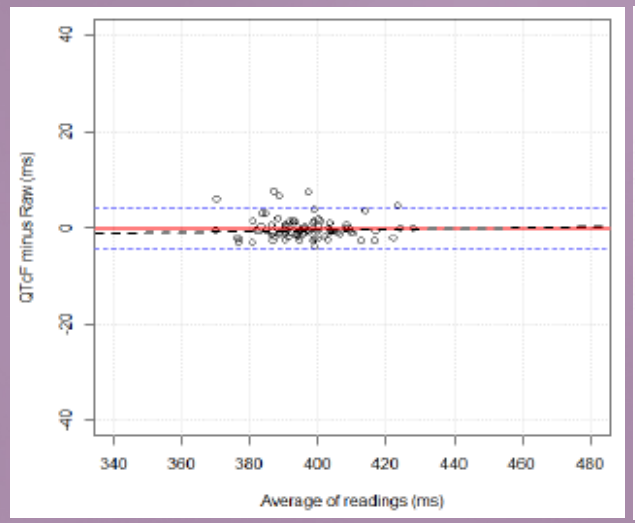
Is bias in QTc data severe to cause false negative results with C-QTc analysis?

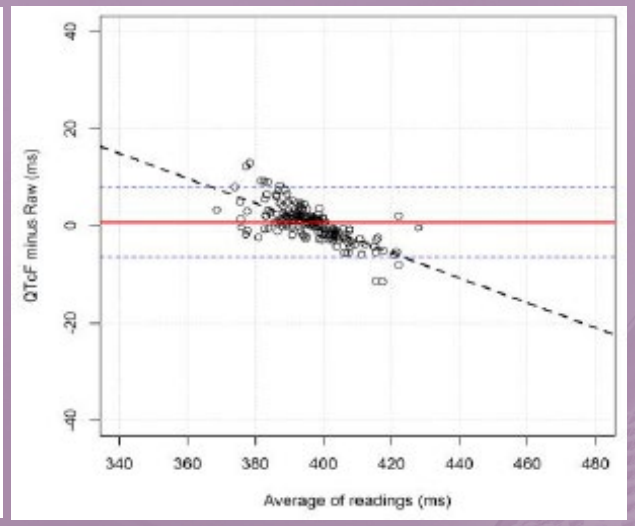
"Fully automated" human independent data

e.g., Bravo (AMPS), Veritas (Mortara), COMPAS (iCardiac), 12SL (GE), Eclysis (AZ) etc.

Comparison using Bland-Altman plot

Core lab "Semi-automated" expert reader data for same study





- Generally, slope < 10 ms per 100 ms acceptable for false negative rate.

Ref: Marathe D., CSRC, 2018;
Darpo B., CSRC-FDA Workshop, 2016;
Ferber G. *et al*, JCP, 2017

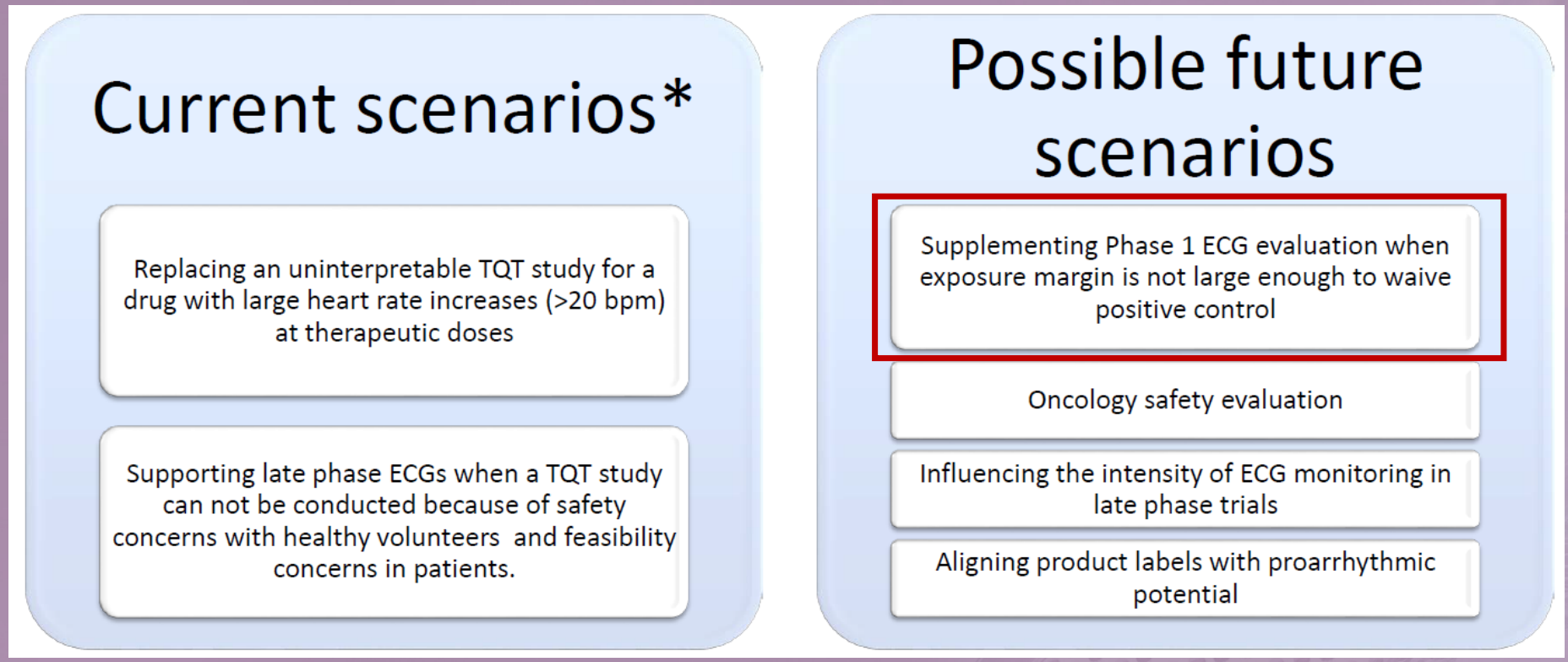
Non-pharmacological approaches (e.g. bias evaluation) as an alternative when desired exposure margin not achieved….achievable

- Only useful for drugs with minimal QT prolongation.
- Relies on accuracy of fully-automated measurements; may be compromised for significant QTc effects / T-wave morphology changes.

- IRT evaluating QT bias on a case by case basis
- Sponsors encouraged to submit such bias analysis if the highest dose in Phase 1 study is marginally failing to meet the exposure margin requirement.

Ref: Marathe D., CSRC, 2018;
Darpo B., CSRC-FDA Workshop, 2016;
Ferber G. *et al*, JCP, 2017;
Johannesen L., CSRC, 2018

Using in vitro data (CiPA assays) to aid clinical development



*FDA has requested CiPA *in vitro* assays with these scenarios

Ref: Garnett C., CSRC, 2018

Omadacycline: in vitro hERG data used in totality of evidence

- **Anti-bacterial; FDA approval in 2018**
- **Background:** Sponsor conducted a TQT study.
- **FDA assessment:**
  - ***TQT is inconclusive:*** Dose-/concentration-dependent increases in heart rate (~17 and 22 bpm) that impacts the ability to interpret QTc effects. Pre-dose/placebo periods did not cover the HR range observed during treatment.
  - ***Clinical data did not suggest risk:*** Phase 3 studies had moxi (a known QT prolonger) and linezolid (no QT effect) as active comparators. No HR effect in patients. Omadacycline QTc signal close to linezolid and much lesser than moxi.
  - ***Robust in vitro safety margin:***
  - hERG IC_{50} / [free C_{max}] is 685 and 484 for doses in TQT study → Higher than current thinking about cut-off value set by the FDA CiPA team [considered low proarrhythmia risk].

Ref: FDA QT-IRT review for Omadacycline;
Omadacycline US Package Insert

Omadacycline: in vitro hERG data used in totality of evidence

- **Outcome:** Totality of data was adequate to inform the label.

FDA Review: …with evolving regulatory thinking about utilizing *in vitro* hERG assay results to bridge information for informing cardiac safety risk when there is a robust safety margin in these assays and a TQT study is either not feasible or not interpretable, we are proposing the labeling…

FDA Label: *Cardiac Electrophysiology*

Based on the nonclinical and clinical data, including electrocardiogram evaluation in the phase 3 clinical trials, one of which had moxifloxacin as a control group, no clinically relevant QTc prolongation was observed at the maximum recommended dose of omadacycline.

Ref: FDA QT-IRT review for Omadacycline;
Omadacycline US Package Insert

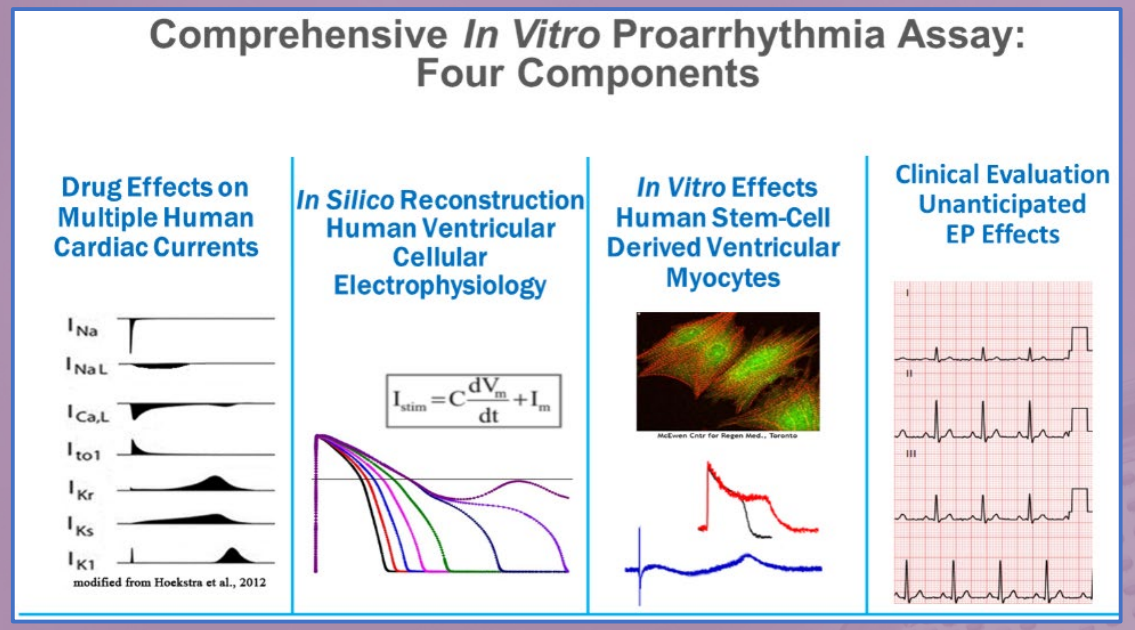
Any approach for de-risking the drug when potential for effects with hERG block likely offset due to multichannel block?

- QTc is currently the best available clinical surrogate for TdP
- QTc has moderate sensitivity for identifying TdP risk, but low specificity
- Some drugs might not be available just based on hERG results
  - *e.g., pentobarbital, verapamil, ranolazine* → multi-channel blockers
- Such drugs with low torsade risk have balanced block of outward current (hERG/iKr) current and inward current (late sodium or L-type calcium block)

Ref: Gintat G, FDA ClinPharm AC, March 15, 2017

CiPA: Approach for de-risking when potential for effects with hERG block likely offset due to multichannel block

- Evaluate proarrhythmic risk using two primary components:
  - *In vitro* drug effects, multiple cardiac channels + *In Silico* reconstruction of cardiac action potential and
  - Confirmation using cardiomyocytes and clinical ECGs



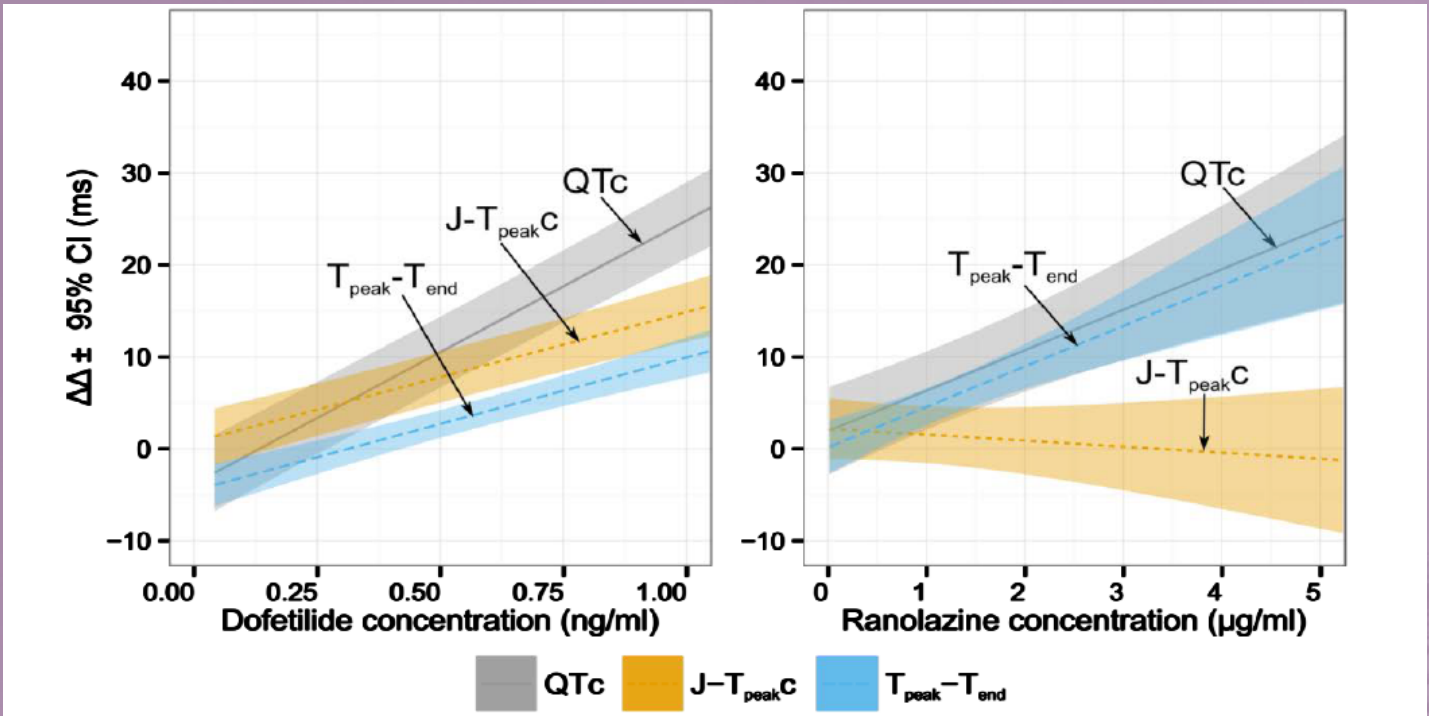
Characterize/Classify Effects

Check for Missed or Unanticipated Effects

Ref: http://cipaproject.org/about-cipa/#About;

Concentration-response analysis for novel biomarkers (e.g., J-T_{peak} interval) may allow distinction for hERG vs. multi-ion channel effects

ECG signatures: hERG vs. balanced ion channel block

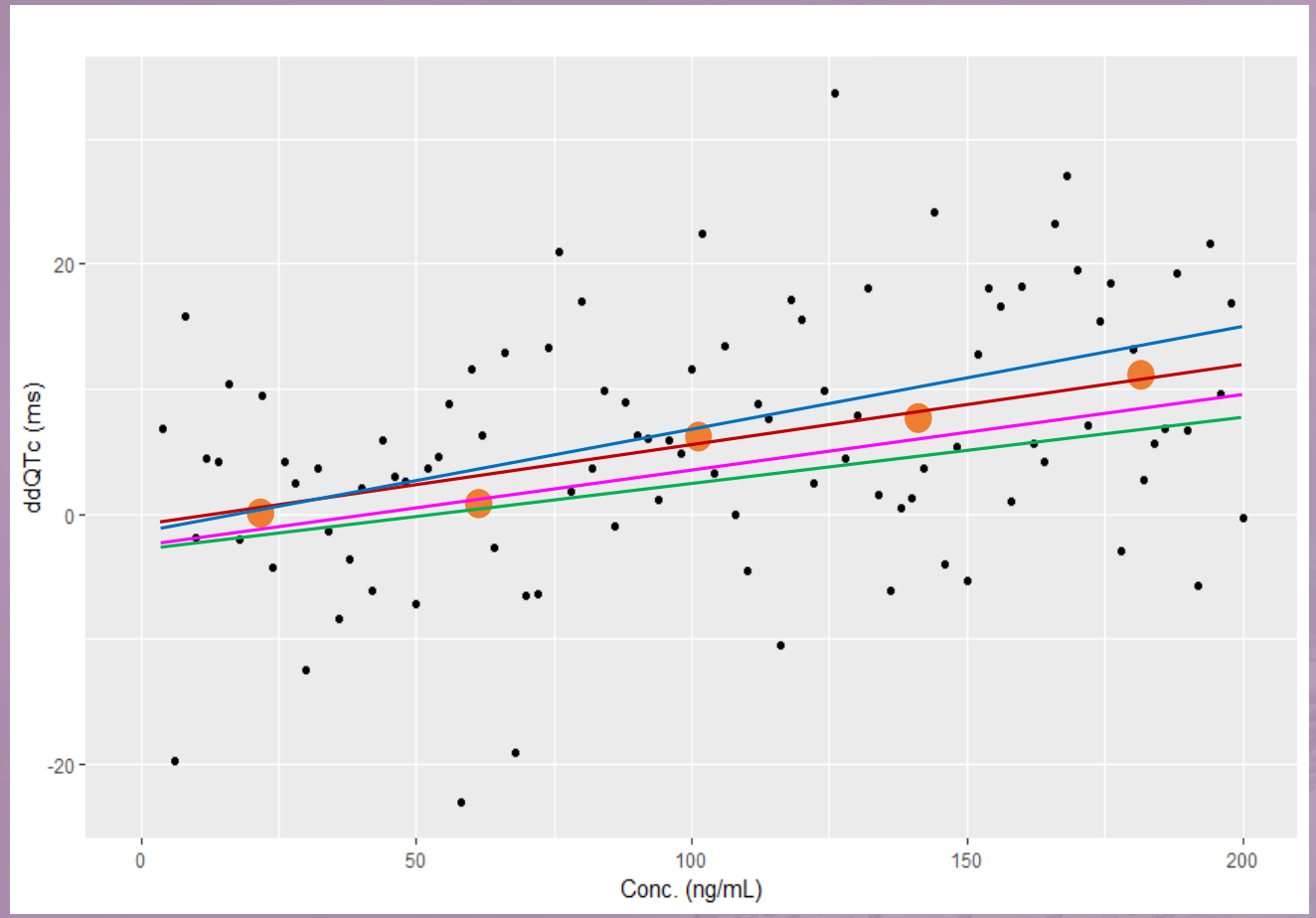


- hERG block prolonged QTc by prolonging J-Tpeakc and Tpeak-Tend
- Balanced ion channel block prolonged QTc by prolonging Tpeak-Tend with no effect on J-Tpeakc

Ref: Vicente JR, *CSRC*, 2018; Johannesen L, *CPT*, 2014

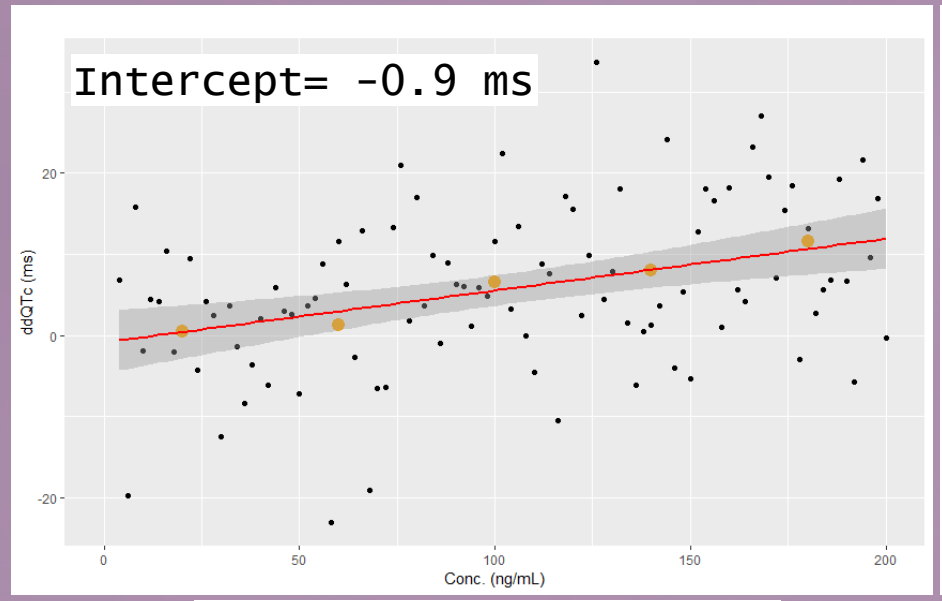
Pointers for analyzing/presenting conc-QTc data

- Scatter plot is not so good for visualization

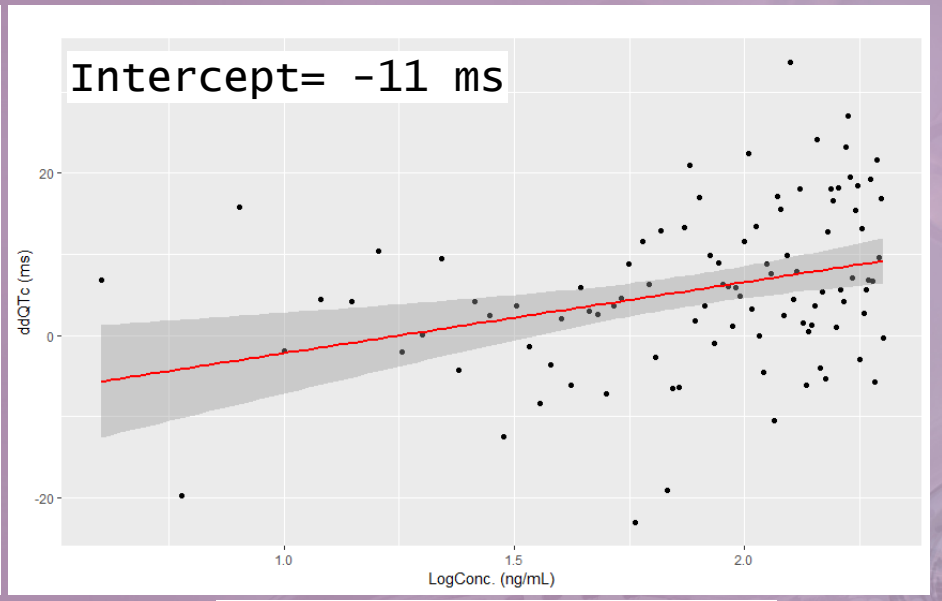


Pointers for analyzing/presenting conc-QTc data

- Avoid using log concentration in C-QTc analysis



Linear Model
Predicted Mean ddQTc
@100 ng/ml → 5.5 ms
@200 ng/mL → **11.9 ms**



Log Model
Predicted Mean ddQTc
@100 ng/ml → 6.6 ms
@200 ng/mL → **9.2 ms**

Contents of QTc submission package for regulatory agency (FDA)

QT evaluation report	
Evaluation report	Include location to evaluation report
Statistical analysis plan	Include location to statistical analysis plan for evaluation report
Investigator's brochure	Include location to Investigator's brochure
Highlights of Clinical Pharmacology and Cardiac Safety	Include location to completed Highlights of Clinical Pharmacology and Cardiac Safety Table (https://www.fda.gov/media/129685/download)
Datasets	Include location to SDTM and ADaM datasets used in the evaluation report. The ADaM datasets should be formatted using the Technical Specification for QT datasets (https://www.fda.gov/media/128187/download)
Analysis programs	Include location to analysis programs used in the evaluation report
Adverse Event analysis	Include location to an Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
Integrated categorical analysis	Include location to an integrated categorical analysis based on all studies included in the QT evaluation report.
Narratives summaries and case report forms	Include location to narratives and case report forms for any of the following: - Deaths - Serious adverse events - Episodes of ventricular tachycardia or fibrillation - Episodes of syncope - Adverse events resulting in the subject discontinuing from the study

Ref: Web Link for FDA IRT site

Contents of QTc submission package for regulatory agency (FDA)

Studies included in QT evaluation *Please add additional rows as needed*				
Study ID	Protocol	CSR	ECG Warehouse ID	ECG collection and analysis methods
Study ID 1	Include link	Include link	Application ID and Study ID used in warehouse upload	Short description of ECG collection (e.g., holter) and analysis methods (e.g., fully-manual or semi-automatic)

Non-clinical studies supporting QT evaluation *Please add additional rows as needed*			
Study ID	Report	Overview file	Raw data
Nonclinical study 1	Include link	If applicable, include link to an overview file, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.	If applicable, include link to Raw and unaltered electrophysiology records (e.g. no baseline subtraction or zero'ing of baseline). The file format for the raw electrophysiology records should be in xls, xlsx or xpt format, and contain at a minimum information about time, voltage and current signals (note specific units for these signals). For current clamp experiments, time and voltage as well as stimulus characteristics.

Ref: Web Link for FDA IRT site

Contents of QTc submission package for regulatory agency (FDA)

Table 1. IRT's Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure		
Maximum tolerated dose		
Principal adverse events		
Maximum dose tested	Single Dose	
	Multiple Dose	
Exposures Achieved at Maximum Tested Dose	Single Dose	
	Multiple Dose	
Range of linear PK		
Accumulation at steady state		
Metabolites		
Absorption	Absolute/Relative Bioavailability	
	Tmax	
Distribution	Vd/F or Vd	
	% bound	
Elimination	Route	
	Terminal t½	
	CL/F or CL	
Intrinsic Factors	Age	
	Sex	
	Race	
	Hepatic & Renal Impairment	
Extrinsic Factors	Drug interactions	
	Food Effects	
Expected High Clinical Exposure Scenario		
Preclinical Cardiac Safety		
Clinical Cardiac Safety		

Ref: Web Link for FDA IRT site

References

- The web-links to references are provided in each slide wherever the content is deemed to be available currently on the web.

Disclosure

- The contents in this talk represent my perspectives and do not necessarily represent the views of any industry or regulatory agency. No official endorsement by these institutions is intended nor should be inferred.