Cardiac Safety Update: Industry Perspective

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Emerging New Paradigm
In Cardiac Safety Assessments

New Cardiac Safety Paradigm

1. Comprehensive In vitro Proarrhythmia Assay (CIPA)
2. Multiple Ion Channel Evaluation (MICE)
3. In silico Predictive Modeling
4. Cell-based Assays – hiPSC-CM
5. Phase 1 Intensive QT (IQT) studies

Non-Clinical QT Assessment CiPA

CiPA: Integrated, Mechanism-based Pro-arrhythmia* Assessment

Ionic Currents / In-silico Based Approach

Effects on Multiple Cardiac Currents (Voltage Clamp Studies)

+

Reconstruction of Cellular Electrophysiology (*In Silico* Studies)

Myocyte-Based approach

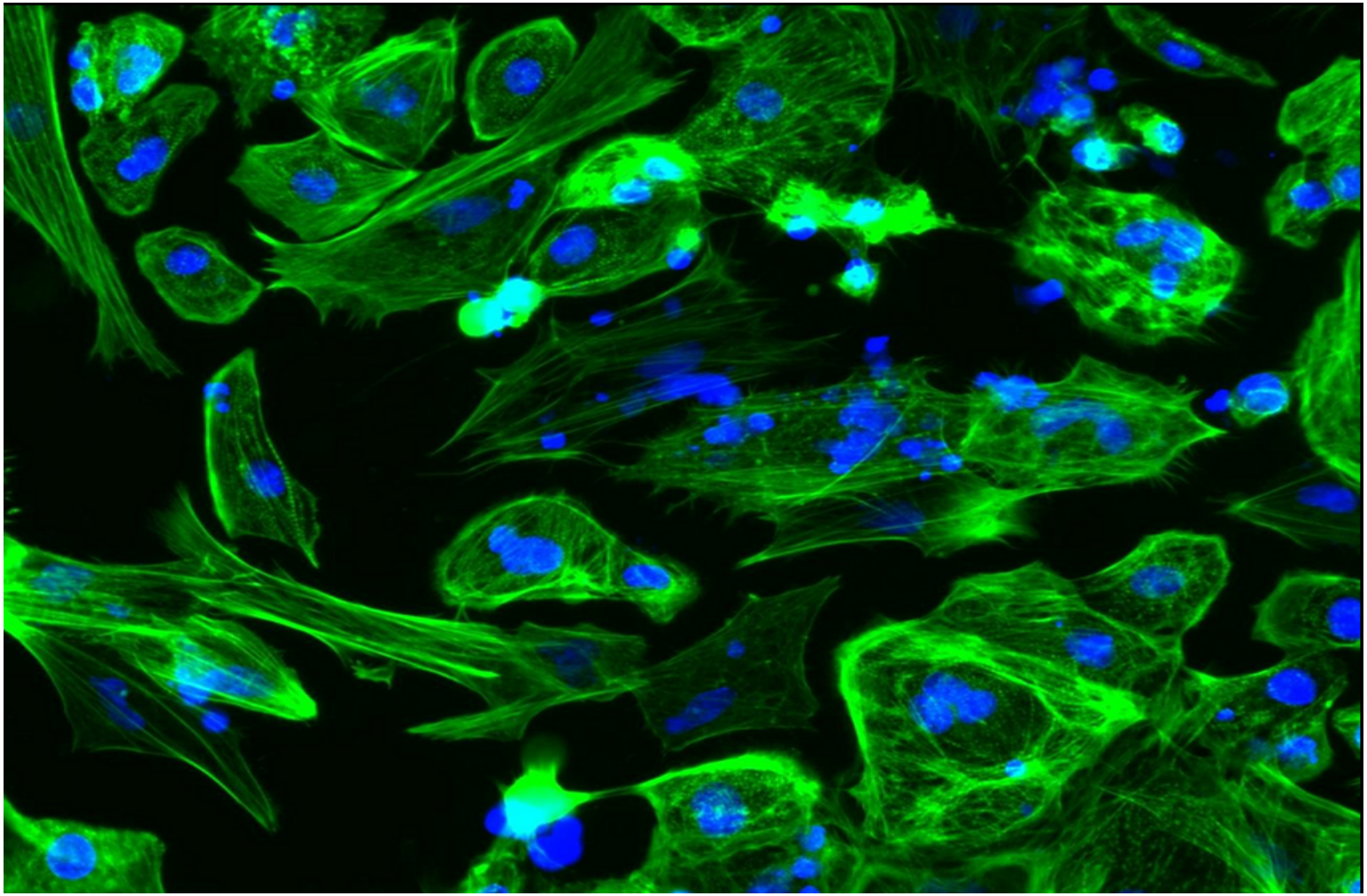
Effects on Human Ventricular Myocytes (*In Vitro* Studies)

* Assays not designed to reproduce arrhythmia

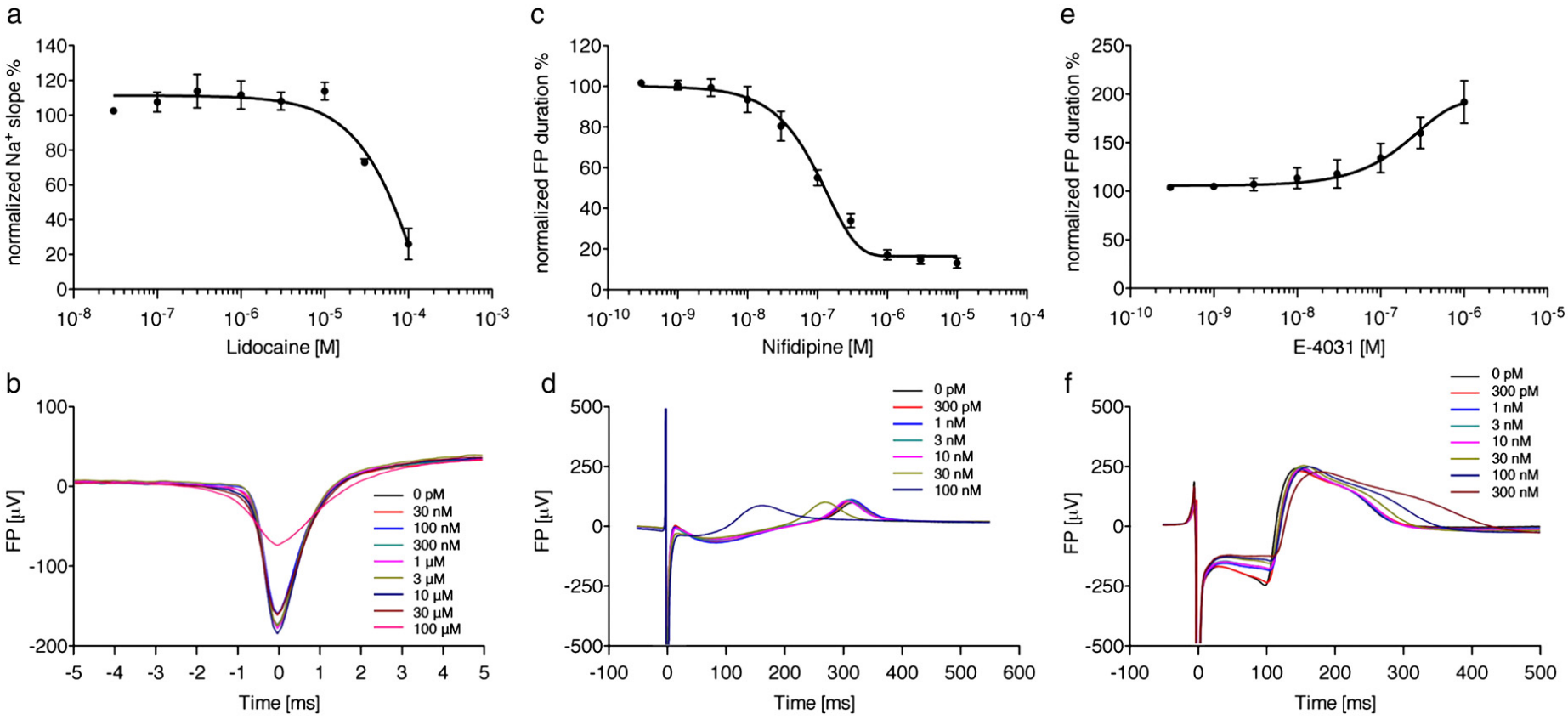
CiPA Development

- **Ion Channels/Voltage Clamp**
  - Channel selection, protocol development, ion current effects for model input (SPS)
- **In-Silico Reconstruction**
  - Model selection and modification, design, execution, feedback and vetting (FDA/Academia)
- **Cell Based Assays**
  - Human stem cell-derived ventricular myocytes, protocols and platforms, validation (Health Environmental Sciences Institute [HESI)
- **Clinical Translation/Regulatory**
  - Drug selection and validation criteria, arrhythmia metrics, ECG assessment (CSRC)
  - Select compound sets for model training and validation (HESI/CSRC)

Human Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CM)



Predicting Drug-Induced Cardiotoxicity Using Human Embryonic Stem Cells



Braam SR, et al. Stem Cell Res. 2010 Mar;4(2):107-16.

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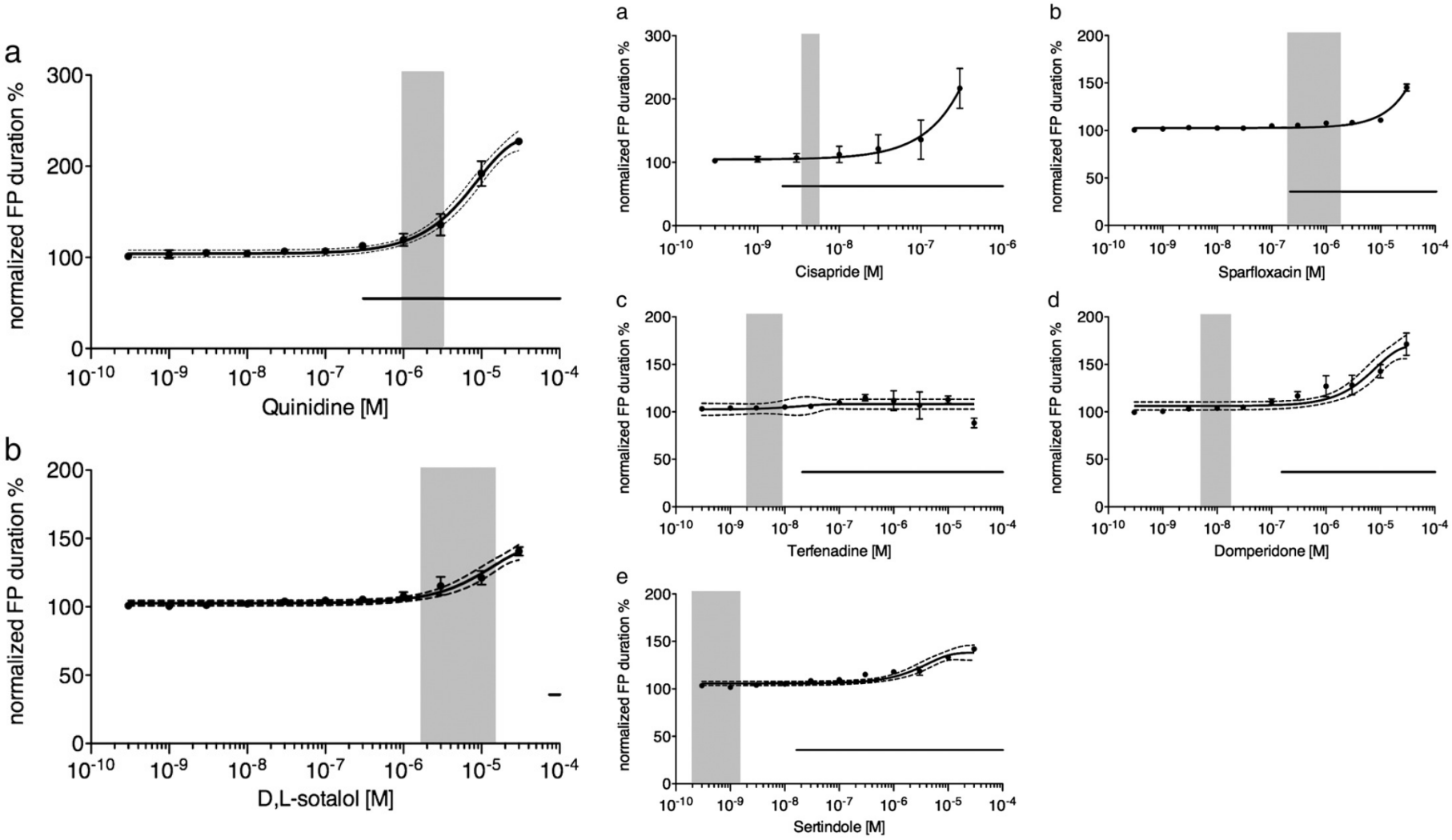

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QT Assessment in Early Development

The IQ/CSRC Proposed Model: Intensive QT (IQT) Assessment

- **Intensive QT (IQT) assessment**

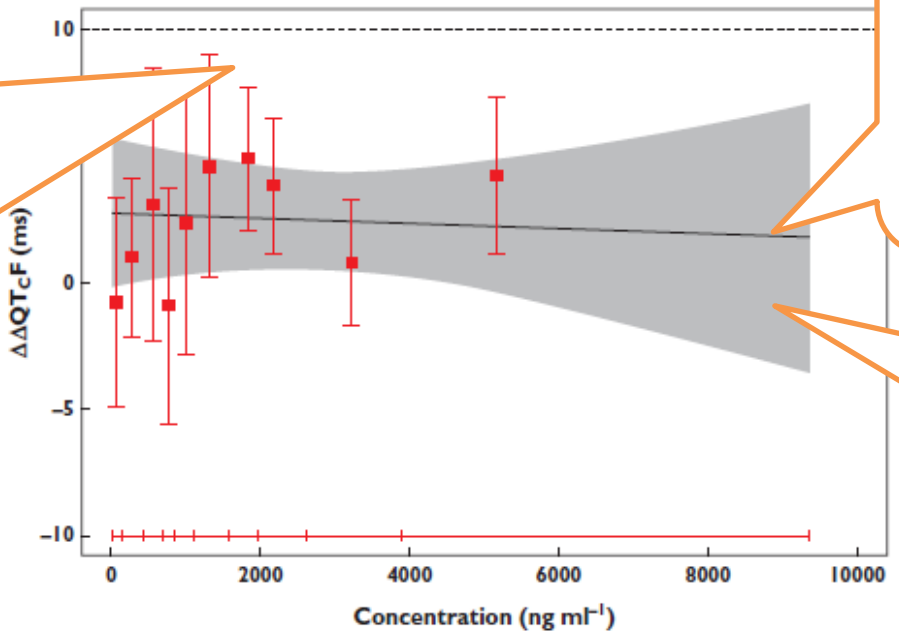
  The proposal is for IQT assessments to be added on routine Phase 1 SAD/MAD studies.

- **Exposure-response Modeling**

  An analysis of the relationship between drug plasma concentrations and QTc (QTc adjusted for placebo and baseline – ΔΔQTc) in Phase 1 SAD and MAD studies.

Exposure-response Modeling
QT Negative Drug

The upper bound of the CI is below 10 ms at each plasma concentration decile



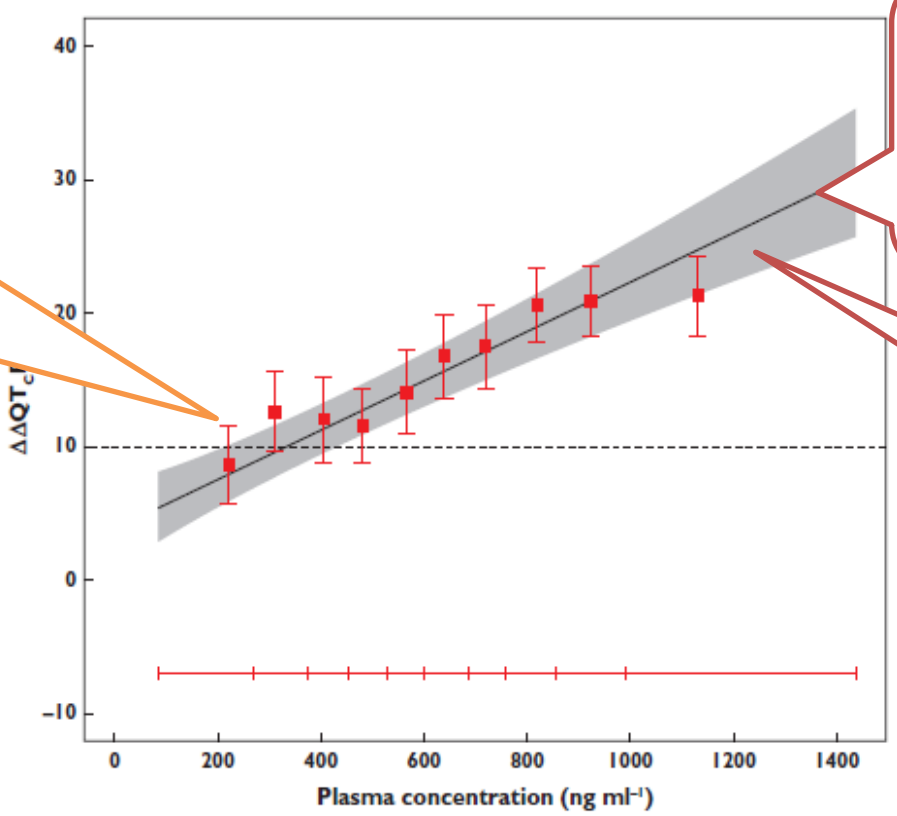
Model based estimates of ΔΔQTc The slope is almost zero

Two-sided 90% confidence interval

Darpo B, et al. Br J Clin Pharmacol 2012; 76:5 / 642–648)

Exposure-response Modeling
QT Positive Drug

The upper bound of the CI exceeded 10 ms at each plasma concentration decile



Model based estimates of ΔΔQTc
Positive slope is apparent

Two-sided 90% confidence interval

Darpo B, et al. Br J Clin Pharmacol 2012; 76:5 / 642–648)

IQ/CSRC Validation Study

- Two organizations - IQ (Consortium for Innovation and Quality in Pharmaceutical Development) and CSRC (Cardiac Safety Research Consortium) – teamed up and initiated a collaborative project to validate an alternative path to quantify QT effects with the objective of replacing the TQT study with this proposed intensive QT (IQT) paradigm.

IQ-CSRC prospective study - Design

- 20 male and female healthy subjects
- 3 treatment periods
- 9 subjects were to receive each drug, 6 on placebo
  - Target to have at least 6 on active and 5 on placebo
- Study drugs:
  - ✓ 5 QT-positive drugs
  - ✓ 1 QT negative
  - ✓ Placebo
- Dosing on 2 days:
  - ✓ Day 1: Dose intended to produce QTc effect of 10 - 12 ms
  - ✓ Day 2: Dose intended to produce QTc effect of 15 -20 ms
- ECG methodology as in TQT studies
- Primary analysis: Exposure Response Modelling

Study Treatments

Drug	Dose	
	Day 1 (Low Dose)	Day 2 (High Dose)
ZOFRAN (ondansetron HCl)	52 mg oral	32 mg given by 15 min IV infusion
QUALAQUIN (quinine sulphate)	648 mg oral**	648 mg q8h x 4
ANZEMET (dolasetron)	100 mg PO** Target Cmax for hydrodolasetron ~ 278 ng/mL.	150 mg IV by 15 min infusion Target Cmax ~ 440 ng/mL
Moxifloxacin	400 mg po**	800 mg IV given by 60 min IV infusion
Tikosyn (dofetilide)	0.125 mg oral	0.25 mg oral
Xyzal (levocetirizine) (negative drug)	5 mg	30 mg

Study Endpoints

Primary endpoint:

- Change-from-baseline QTcF (ΔQTcF)

Secondary endpoints:

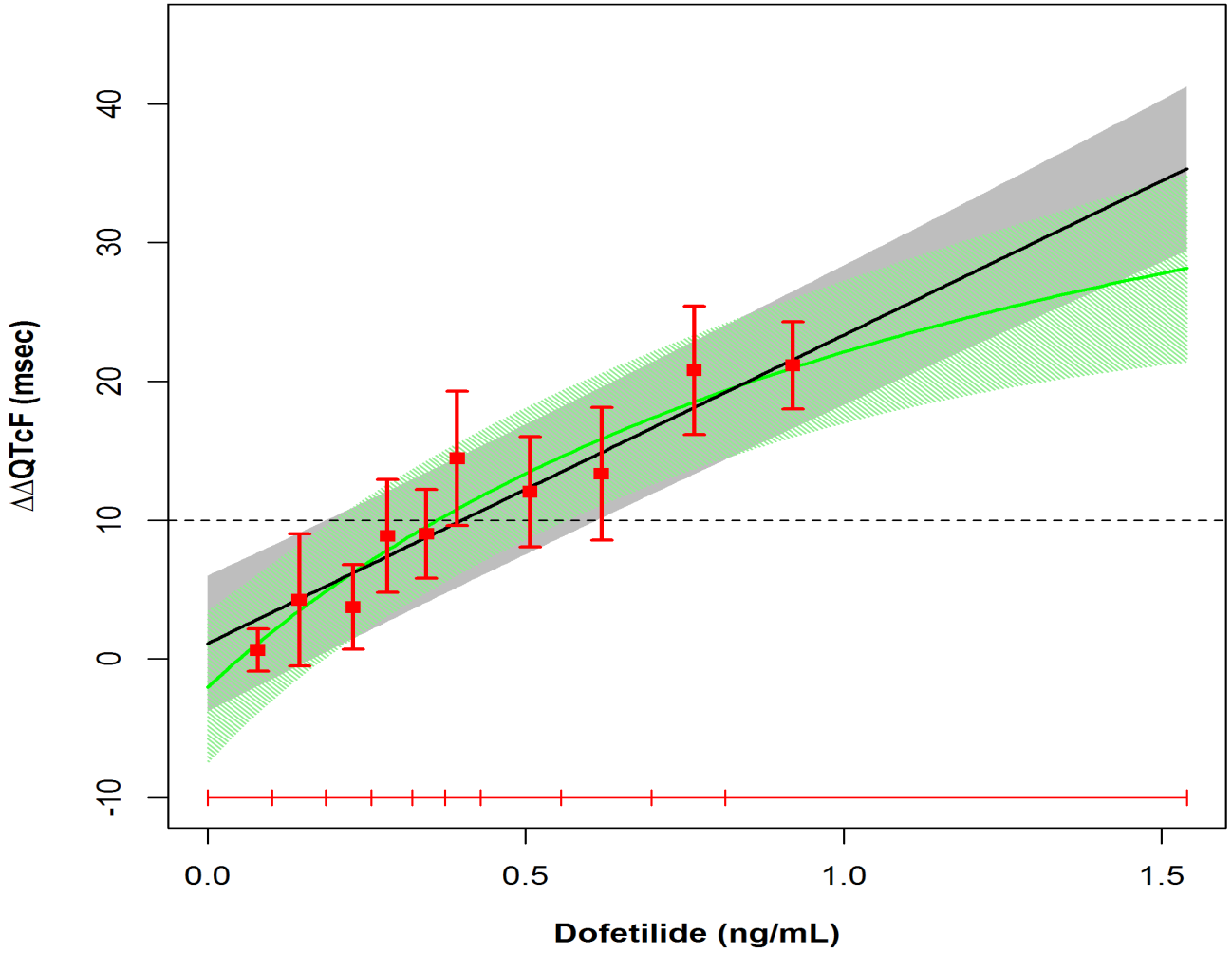
- ΔΔQTcF by time point
- Categorical analysis of the QTc outliers
- Effects on heart rate, PR and QRS intervals.

Top Line Results

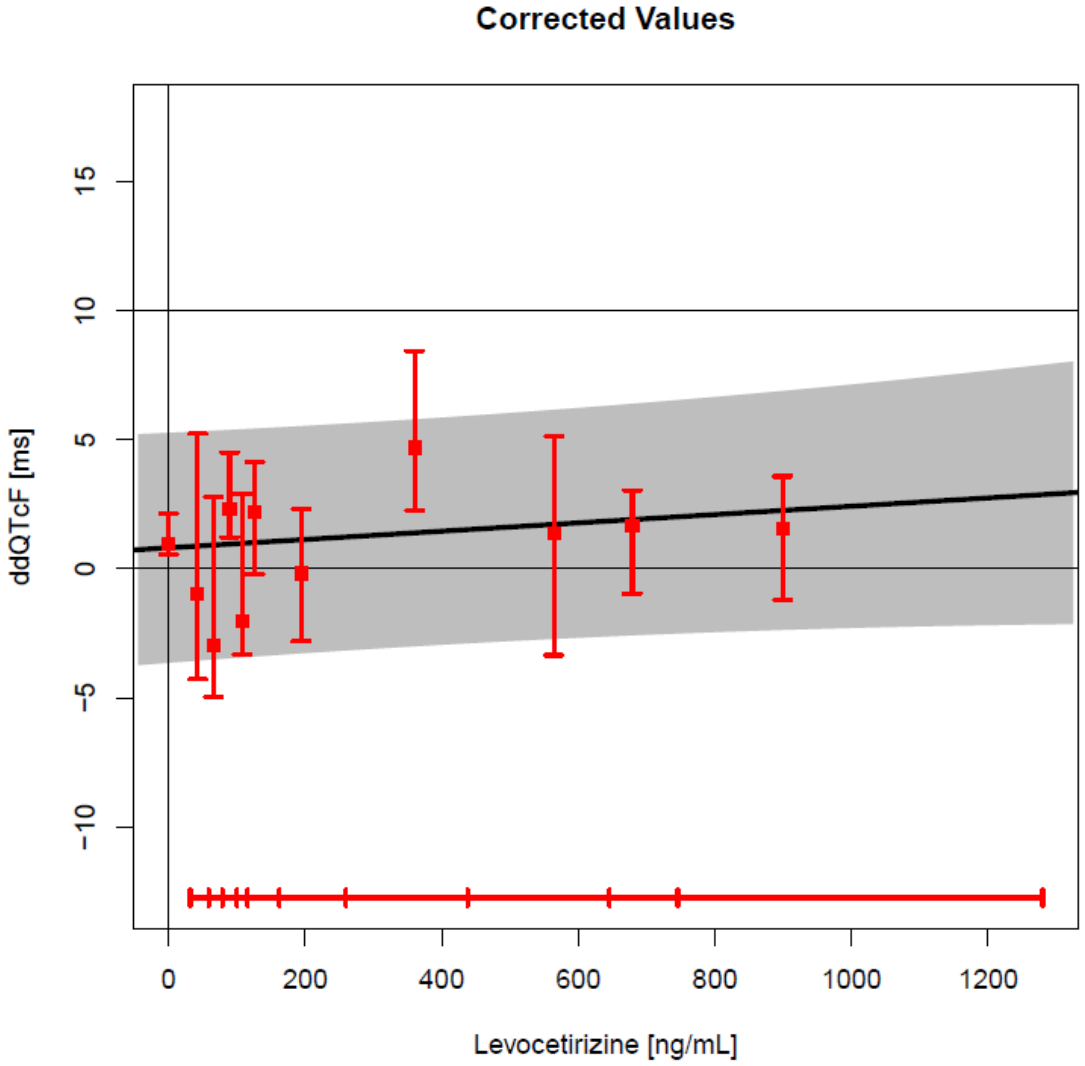
- All 5 positive drugs met the pre-specified criteria , i.e. the study was able to demonstrate a drug-induced QT effect at the dose identified by FDA

- The negative drug, levocetirizine, also met the criterion, i.e. a QT effect above 10 ms could be excluded

Dofetilide - Exposure Response Analysis



Levocetirizine - Exposure Response Analysis



IQ/CSRC Study Limitations

- Drugs with borderline QT effect
- Drugs with long T1/2
- Drugs with delayed effects
- Drugs requiring up-titration
- Drugs with active metabolites
- Drugs with known autonomic effects
- Drugs associated with QT:RR hysteresis
- Any drugs requiring parallel group design

Challenging Tasks for ER Relationship in Early Phase QT Assessment

- Demonstrate assay sensitivity without using a pharmacological positive control.
- Achieve sufficient power to clear the E14 primary end-point – Upper 95% CI < 10 msec.
- Exhibit sensitivity and specificity to identify both false positive and false negative effects
- Meet current regulatory expectations with a much lower number of subjects in a IQT study compared with a TQT study.

Shifting Cardiac Safety Paradigms

Current

- ***S7B: In Vitro*** **IKr Assay**
- ***S7B: In Vivo*** **QT Assay**
- **E14: Thorough QT/QTc Study**

Future

- **Comprehensive in-vitro Pro-arrhythmia Assay (CiPA)**
- **Multiple Ion Channel Evaluation (MICE)**
- **Intensive QT Study (ER Analysis)**
- **Thorough QT/QTc?**

Clinical Outcome

- **Torsades de pointes**
- **Sudden Cardiac Death**

Future of Early Phase QT Assessment

- Intensive (SAD/MAD) QT studies where appropriate
- Consider TQT study when an IQT design is not a good option
- Other approaches using standard development studies

- Rule out QT prolongation based on robust evidence, or
- Accept QT prolongation based on robust evidence

Thank You For Your Attention