IQ-CSRC Prospective Study
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Background and Objectives

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Borje Darpo MD, PhD

iCardiac Technologies

Co-chair SoC, CSRC

Objectives of the IQ-CSRC Prospective Study

The objective of the initiative was to evaluate whether QT assessment in early phase clinical studies can replace or serve as an alternative the TQT study

- We therefore conducted a prospective clinical study in healthy subjects with design similarities with a standard FIH study
- The underlying idea is to apply exposure response (ER) analysis on robust ECG data from early phase clinical studies without change in standard design
- Collaborative project between the IQ-consortium, CSRC and FDA
- Design of study, selection of drugs and doses and statistical analysis discussed and agreed upon with FDA

Background of the IQ-CSRC Prospective Study

This study is a consequence of activities that have been on-going for several years

- Extensive experience has been gained in FDA by applying ER analysis on TQT study and patient data through centralized (IRT) review of QT studies
  - Good correlation between predicted QT effect in the 'by timepoint' analysis and the ER analysis
- Increasing comfort among sponsors with ECG assessment in early phase clinical studies
- *Optimized QT group* formed 2009 by pharmacometricians to study and promote ER analysis for QT assessment

CSRC-IQ Steering Committee

IQ Consortium Clinical Pharmacology Leadership Group

- Nenad Sarapa (Bayer)
- Venkat Jarugula (Novartis)
- Jim Keirns (Astellas)
- Charles Benson (Lilly)

CSRC

- Christine Garnett (Certara)
- Borje Darpo (iCardiac)
- Catherine Ortemann-Renon (Sanofi)
- Corina Dota (AstraZeneca)

OQT Working Group (SAP)

- Steve Riley (Pfizer)
- Georg Ferber (Consultant)

- **DCRI**
- Cindy Green

FDA

- Kevin Krudys
- Lars Johannesen

FDA: Norman Stockbridge, Jiang Liu + many others.
Covance: Randall Stoltz
iCardiac: Meijian Zhou, Brian Smith
CSRC: Valarie Morrow, Princess Grimes

What's wrong with the TQT study?

- Probably nothing, if seen as a screening tool that must identify all drugs that prolong the QT interval, i.e. very sensitive
- The combination between the 'by timepoint' analysis (IUT) and the objective to exclude a QT effect >10 ms, has however rendered the study low specificity
- If the same data can be generated from a standard early phase clinical pharmacology study, this would represent a more efficient approach and also have other advantages (e.g. liability known early on)
- Vast majority of drugs that cause TdP do this based on concentration dependent QT prolongation - exposure response (ER) analysis of QT effect therefore makes sense biologically
- Early clinical phase QT assessment generates QT data with same high level of confidence as the TQT study, i.e. is not contingent upon changed non-clinical paradigm

Top Line Results

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

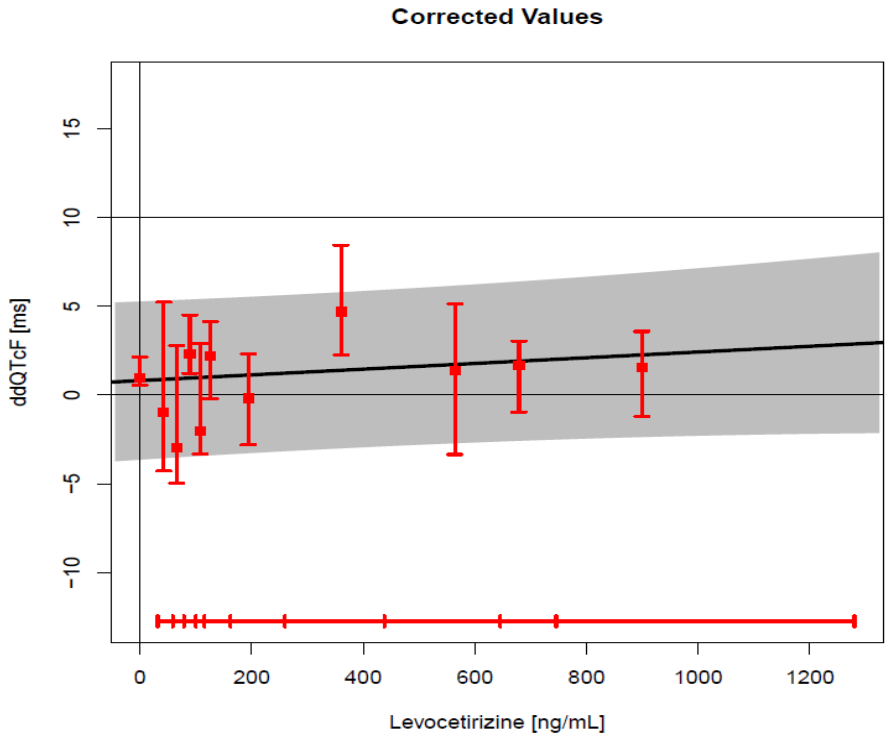
- The negative drug, levocetirizine, also met the criterion, i.e. a QT effect above 10 ms could be excluded

Our proposal for QT assessment in early phase clinical studies

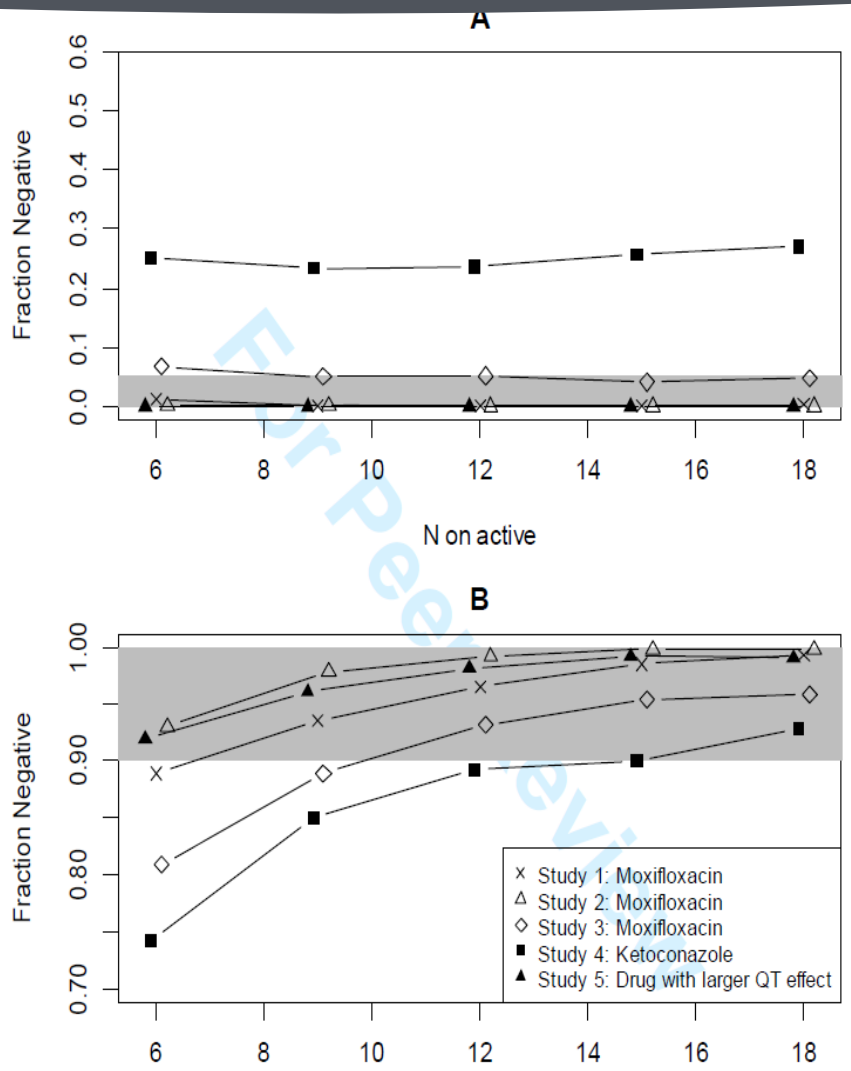
We propose using the same criteria as in the ICH E14 for QT assessment adapted to exposure response analysis:

Criteria for negative QT assessment:

The upper bound of the 2-sided 90% confidence interval (CI) of the predicted placebo-adjusted ΔQTcF is below 10 ms at clinically relevant plasma levels of the drug.



Rate of false negatives based on simulated small studies



- 15,000 small studies with 6 – 18 subjects on active and 6 on placebo simulated on TQT study data
  - ✓ Moxifloxacin; 3 TQT studies
    Peak ΔΔQTcF: 12.5, 14.0 and 8.0 ms
  - ✓ Ketoconazole, 1 TQT study
    Peak ΔΔQTcF: 7.6 ms
  - ✓ Drug with large QT effect; 1 TQT study
    Peak ΔΔQTcF 25.9 ms
- Rate of a false negative results is around 5% or substantially lower with 6 on active when a drug like moxifloxacin is evaluated.
- This risk seems lower than the historical failure rate of the moxifloxacin assay sensitivity test in TQT studies.

Panel A: rate of false negatives with drug data;

Panel B: Rate of false positives using placebo data and time-matched PK data

Ferber, Zhou and Darpo. Detection of QTc effects in small studies - Implications for replacing the thorough QT study
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Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase

Borje Darpo*, MD, PhD[1,2], Charles Benson[#], MD, PhD[3], Corina Dota*, MD[4], Georg Ferber, PhD[5], Christine Garnett*, PharmD[6], Cynthia A Green, PhD[7], Venkateswar Jarugula[#], PhD[8], Lars Johannesen, MSc[9], James Keirns[#], PhD[10], Kevin Krudys, PhD[11], Jiang Liu, PhD[11], Catherine Ortemann-Renon*, PharmD, PhD[12], Steve Riley, PharmD, PhD[13], Nenad Sarapa[#], MD[14], Brian Smith, BS[2], Randall R Stoltz, MD[15], Meijian Zhou, PhD[2], Norman Stockbridge, MD, PhD[16].

*: Representing the Cardiac Safety Research Consortium (CSRC);
[#]: Representing the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ);