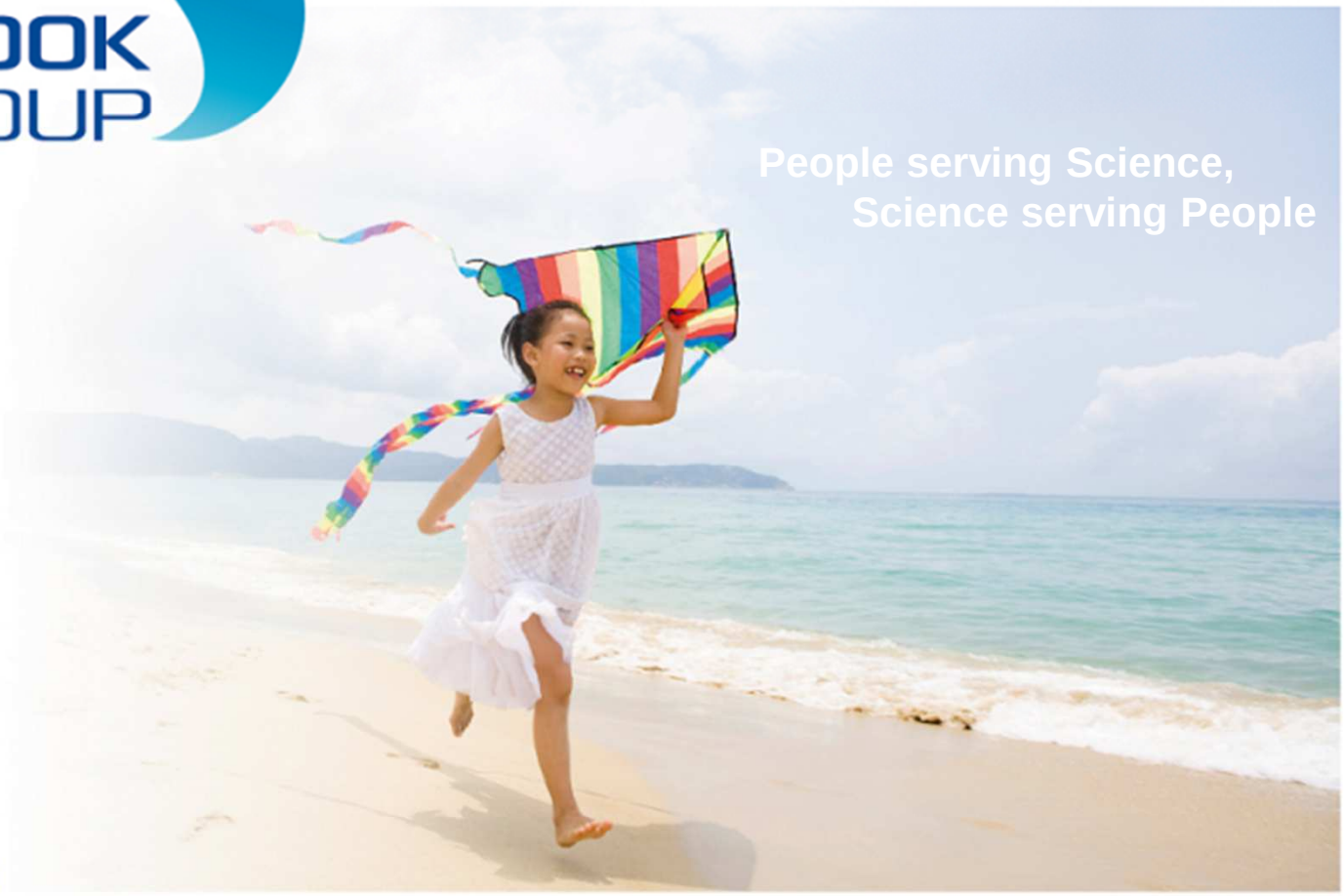
BANOOK GROUP



CARDIAC SAFETY

CENTRAL IMAGING

ENDPOINT ADJUDICATION

Club de Phase 1 – 22 MAR 2016 – Paris

Pascal Voiriot (Nancy) & Pierre Maison Blanche (Paris)

CARDIAC SAFETY

Early Phase 1 QT assessment as an alternative to Thorough QT studies

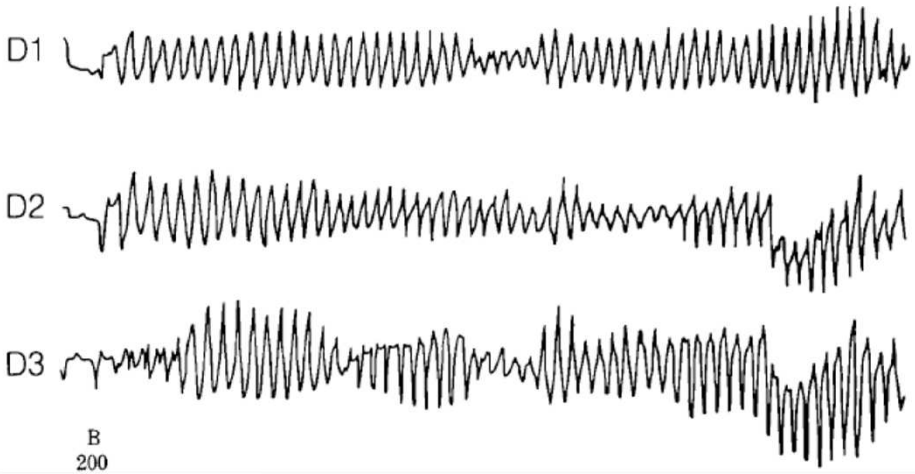
Changing Regulatory Landscape

BANOOK GROUP

1° WHAT IS THE CONCERN ?

The concern is the occurrence of a <u>sudden death</u> following a drug intake: ~10% of total deaths

For small molecules (<1000d), a cause leading to a sudden death is the occurrence of a « Torsade de Pointe »

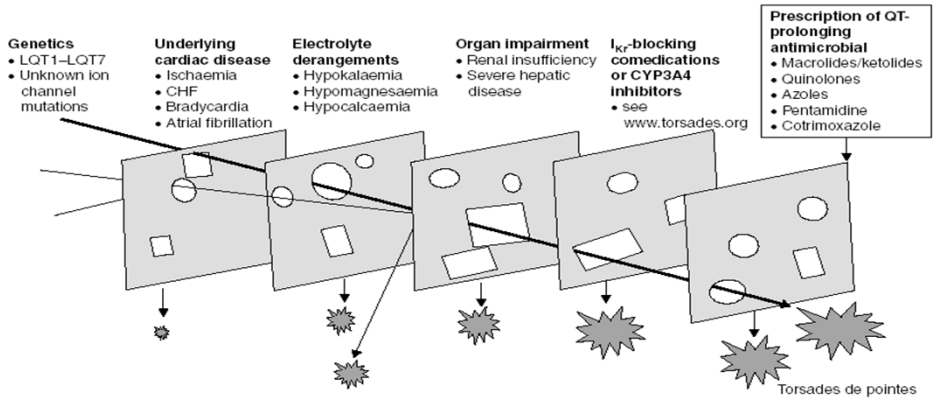


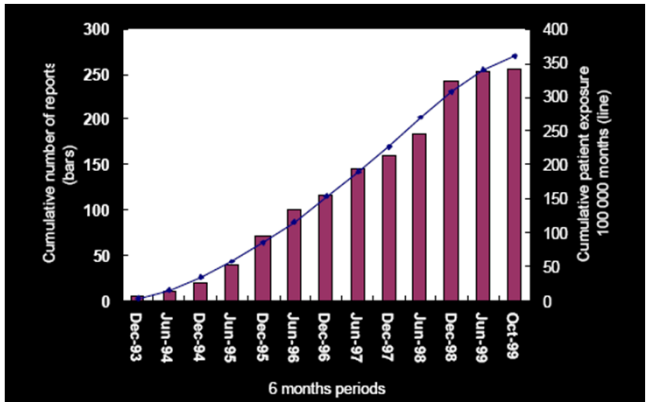
Torsade de Pointe, as originally described by Dessertenne (1962)

2° WHAT IS THE ISSUE ?

TdP is a rare event: ~1/1000 of the “sudden deaths”

• General population (w/o drug exposure):	8-10 events/10 millions/year	(0.0001%)	(base 1)
• Non cardiovascular drug:	40 to 100 events/10 millions	(0.001%)	(~*4 to 10)
• Oncology drugs (NAA):		(up to 2%)	(~*2000)
• Anti-arrhythmic drugs:	10^4 to $4*10^4$ events/10 millions	(up to 4%)	(~*4000)





According Cisapride database, one TdP for ~100 000 “months of treatment”
Indeed, a “surrogate of TdP” had to be defined for drug development:
And the surrogate is ….. The QT interval prolongation after drug exposure

In other words, QT prolongation “per se” is not a (serious) clinical event: QT interval prolongation is only a “surrogate”

3° WHAT WAS THE REGULATORY ANSWER ?

ICH « QT » 2005 Guidelines for « QT » Safety Pharmacology

S7B : The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) By Human Pharmaceuticals

This guideline describes a **non-clinical testing** strategy for assessing the potential of a test substance to delay ventricular repolarization.

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

Guidance to sponsors concerning the design, conduct, analysis, and interpretation of **clinical studies** to assess the potential of a drug to delay cardiac repolarization.

With the following information:

« When additional data (non-clinical and clinical) are accumulated in the future, this document may be reevaluated and revised »:

And it was done four times:

- ***ICH E14 Q&A JUN2008***
- ***ICH E14 Q&A APR2012***
- ***ICH E14 Q&A MAR2014***
- ***ICH E14 Q&A DEC2015***

4° WHAT ARE THE « E14 GUIDANCE » CORNERSTONES

Population Risk Assessment

(primary endpoint)

Central tendency

- <5msec: no regulatory risk
- >20msec: « concern »
- 5-20??? (warning in RCP)

Two sided $^{90\%}$CI: upper limit

- **10msec (usual)**
- 20msec (oncology)

Individual (categorical analysis)

(secondary endpoint)

Relevant QTc thresholds

- QTc>450msec
- QTc >480msec
- QT/QTc>500msec (« concern »)

Change from baseline

- <30msec (noise/Δ circad)
- >60msec (« concern »)

Accordingly, a «QT waiver» can be claimed if the following criteria are met:

1. ***Demonstration of assay sensitivity for QT assessment (pre-requisite)***
2. ***Upper limit two-sided $^{90\%}$CI < 10msec ("by time point" analysis/intersection-union test) (primary endpoint)***
3. ***Lack of issues regarding secondary endpoints including:***
   - *categorical analysis*
   - *consistent PK/QT PD analysis (concentration-ECG response modeling)*

5° 12 YEARS LATER, PRO & CONS ?

>>500 TQT studies since 2005

FDA feed back on ~ 300 TQT studies data reviewed by the agency (N. Stockbridge – 2014)

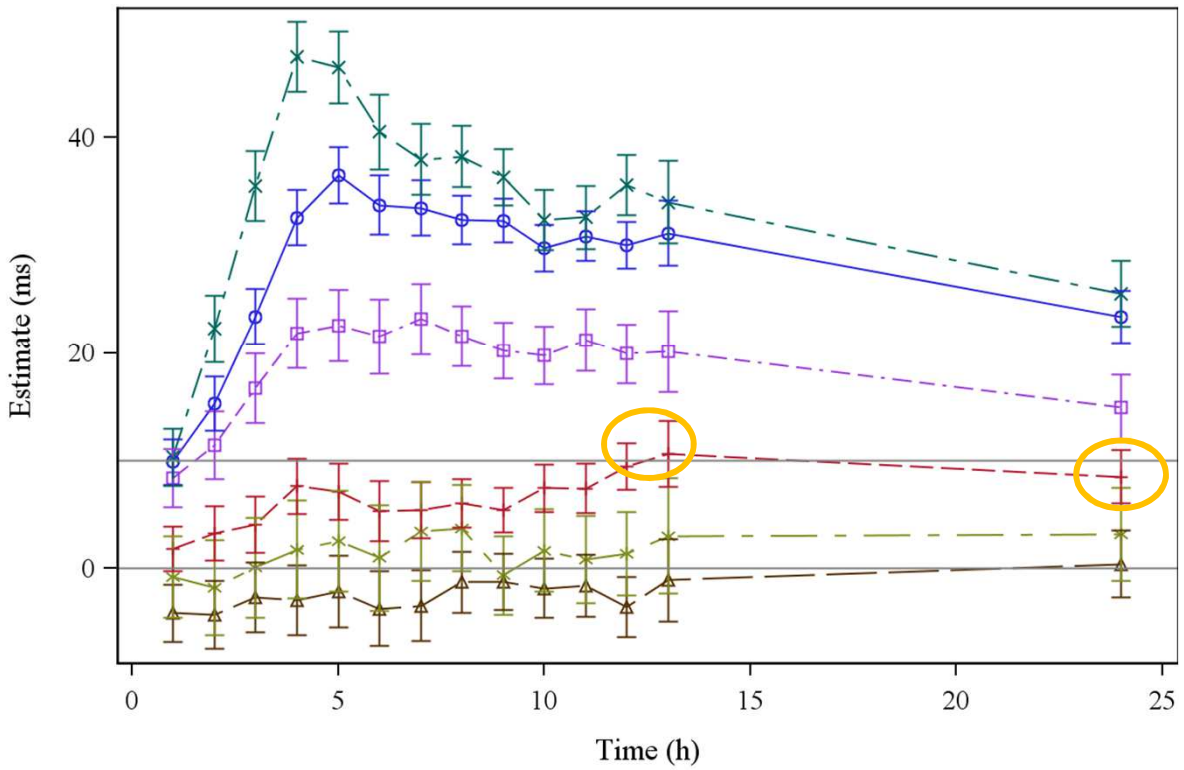
Pro

- **For agencies**
  - ❑ No longer QT-related withdrawal
  - ❑ Reduction in post-marketing reports of TdP for non-anti-arrhythmic drugs
  - ❑ Continued to approve some drugs with QT liability where benefits clearly outweigh apparent risk
- **For developers**
  - ❑ « Play rules » and well known design
  - ❑ Fewer model assumptions
  - ❑ Well known network of qualified vendors

Cons

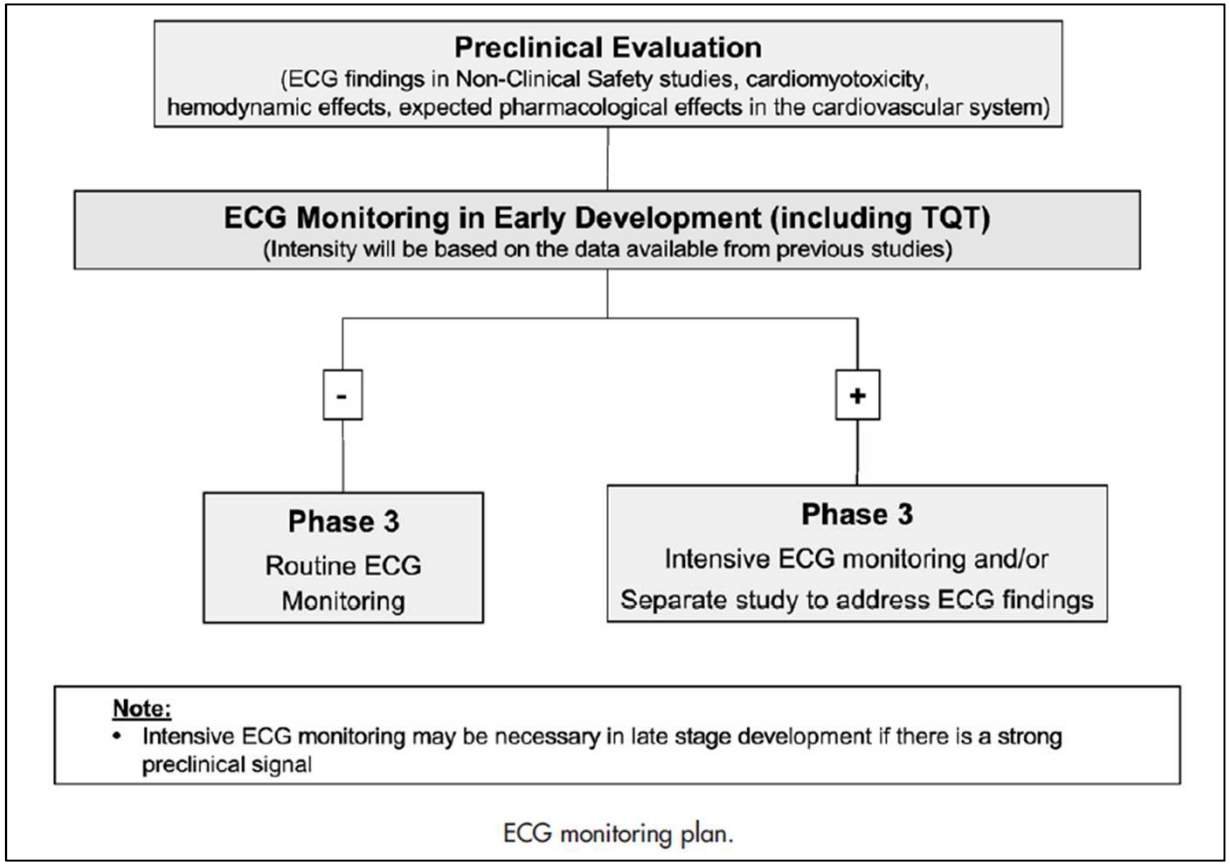
- **For agencies (few … but important)**
  - ❑ Perversion of lead candidate selection (selection against hERG)
- **For developers (a lot …)**
  - ❑ Cost: need for a dedicated expensive study (as a glance, FDA said « $B »)
  - ❑ Late in the development (need for an “in-depth” knowledge of the drug pharmacology including accumulation, DDI and metabolites profile…)
  - ❑ Uncertain « pre-test » hypothesis: conservative sample size for ensuring an acceptable power
  - ❑ Focus on a single timepoint (repeated)
  - ❑ Sensitive to outliers (sometimes « unfair »): sponsor may be punished for adding a timepoint

« BY-TIMEPOINT ANALYSIS »: EXAMPLE WITH ANTIMALARIAL DRUGS



- « QT liability »
- QT ?
- « QT waiver »

DECISION-MAKING FOLLOWING TQT STUDY ANALYSIS



ECG monitoring plan during clinical drug development (***Rodriguez I et al; Am Heart J. 2010)***

6° INITIATIVES LEADING TO THE ICH-E14 NEW PARADIGM?

First step (2010-1014)

- Pfizer and AZ's review of internal data
- Review of "moxi" arm results for agreement between « per timepoint analysis » and the « concentration-ECG response modeling » for QT assessment (J Florian et Al, Journal of Clinical Pharmacology, 2011)
- CSRC (Cardiac Safety Research Consortium) brainstorming
- Questions to ICH committee

→ *Answers of ICH committee (ICH E14 Q&A **Mar2014**)*

Second step (2014-2015)

- CSRC published a white paper on "replacing the TQT Study" (FDA, EMA, EFPIA and PhRMA co-authors)
- IQ-QT study (CSRC initiative)
- Results of IQ-QT study and questions addressed to ICH-E14 committee

→ *Answers of ICH committee (ICH E14 Q&A **Dec2015**)*

7° WHAT IS THE « NEW » QT ASSESSMENT PARADIGM (IN 2016)

ICH E14 (with Q&A update) remains the guidance in force for the drug developers

First major change:

- ***Before Dec2015***
  - ❑ **the "by-timepoint analysis" or "intersection-union test" was the mandatory primary endpoint to consider for decisions** to classify the risk of a drug.
  - ❑ All other analysis (categorical analysis, ECG PK/PD modeling) even considered as part of the analysis, were actually **secondary endpoints** only
- ***Since Dec2015***
  - ❑ **"Concentration-ECG-response analysis" can serve as an alternative (primary endpoint), for decisions to classify the risk of a drug.**

Second major change:

- ***Since Dec2015**, depending on the primary endpoint chosen:*
  - ❑ **The "by-timepoint analysis" always requires a dedicated TQT study** with a positive arm, a supra-therapeutic arm and an appropriate sample size (for power needs)
  - ❑ **Conversely, the "concentration-ECG response modeling" :**
    - Always can be given from a TQT dedicated study (interest: less "punishing")
    - But **there is no longer a mandatory requirement** for considering data issued from a dedicated **TQT study**, nor even a single study…

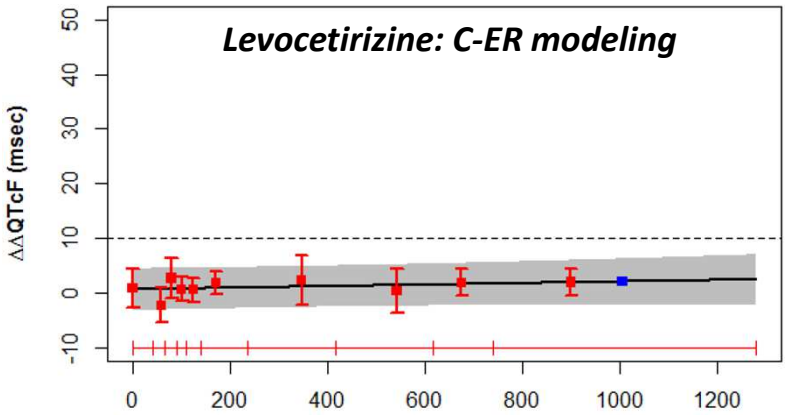
8° C-ER: NO NEED FOR A DEDICATED STUDY ???

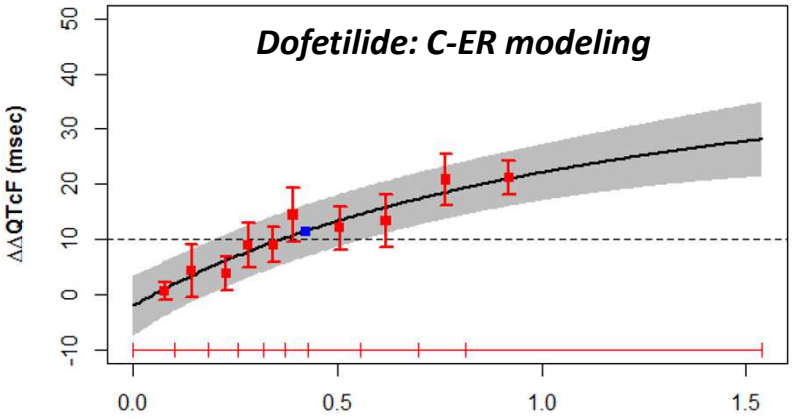
Data can also be acquired from:

- first-in-human studies,
- multiple-ascending dose studies (metabolites …),
- or other studies.

Additional data would be useful to ensure information on exposure well above the exposure at the maximum therapeutic dose, to cover the impact of:

- accumulation with repeated dosing,
- drug-drug and drug-food interactions,
- organ dysfunction,
- genetically impaired metabolism. …





9° SPECIFIC REQUIREMENTS FOR ACCEPTABLE C-ER ?

High quality ECG collection & reading, as for a "dedicated" study:

- Same ECG time points/ same PK samples
- Digital triplicates, extracted
- Centralized blinded analysis

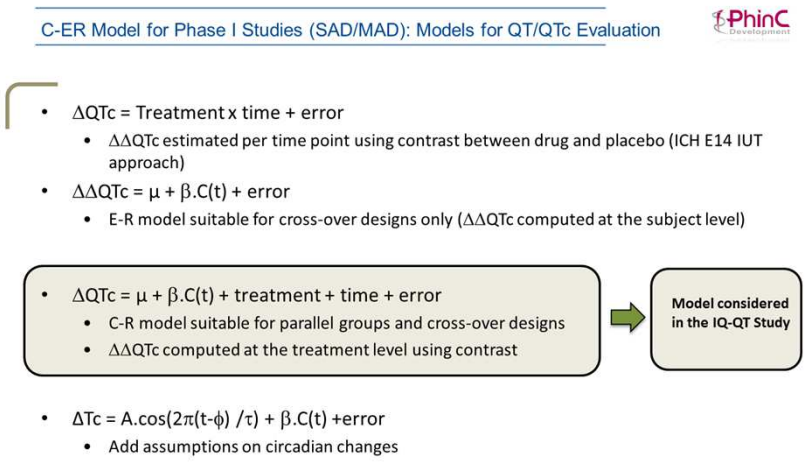
Concentration-response analyses of the same data using models with different underlying assumptions **can generate discordant results**.

Hence there are regulatory requirements specified in the release of E14 Q&A Dec2015:

- **For specifying prior to analysis** to limit bias**:**
  - **Modeling methods and assumptions,**
  - **Criteria for model selection,**
  - **Rationale for model components,**
  - **Potential for pooling of data across studies**

- **For appropriately documenting:**
  - **Testing for model assumptions,**
  - **Hysteresis**
  - **Goodness of fit**

.

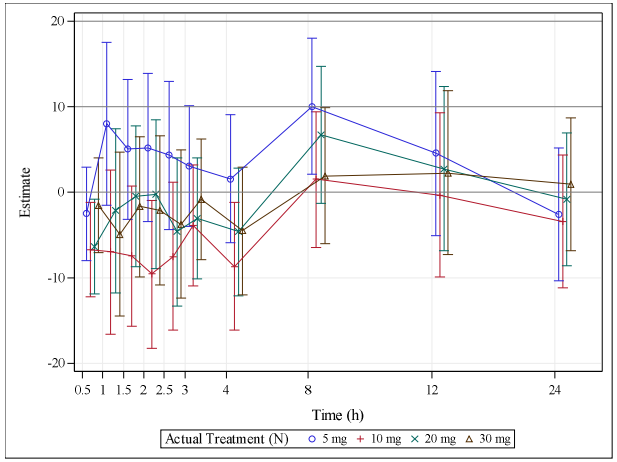


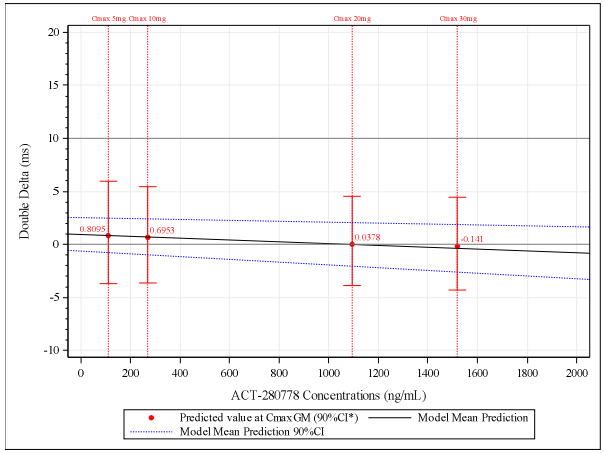
10° E14 Q&A Dec2015: HYPOTHESIS AND THRESHOLD FOR DECISION-MAKING?

As for “by-time-point analysis”, if using a “C-ER modeling” as the primary basis to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for the QTc effect should be **<10 ms** at the highest clinically relevant exposure.

Both the “by-time point” analysis (TQT analysis) and the C-ER modeling estimate the maximum effect of a drug treatment on the QTc interval, but **they are not used to test the same hypothesis**.

Hypothesis testing based on a “by-time point analysis” is inappropriate in studies designed for a C-ER modeling, if **not powered to assess the magnitude of QT prolongation** for each time point.

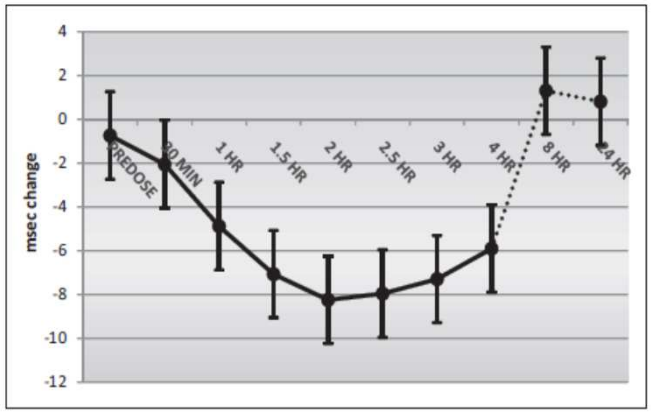




11° ASSAY SENSITIVITY AND C-ER MODELING ?

<u>Before Dec2015</u>, according ICH E14 Mar2014,

- the regulatory position, was: "in the absence of a positive control, there is a reluctance to draw conclusions of lack of an effect … "
- indeed, for phase 1 studies targeting a subsequent C-R analysis, we suggested the following :
  - ❑ In case of expected QT liability (QT effect), no assay sensitivity assessment
  - ❑ If a QT waiver is expected, performing an assay sensitivity assessment
    - "Moxy"day
    - Meal effect
    - Gender difference (in case of males & women involvement)



Food effect on QTcF with $^{95\%}$CI

When corrected, QTcF interval was shortened significantly (-8,2msec) with the maximal effect observed at 2 hours after dose

from Taubel - 2015

<u>Since Dec 2015</u>, regulatory position is more clear (ICH E14 Q&A -12/2015) :

- "*If* there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure, (then) a **separate positive control would not be necessary**"
- Indeed, the assay sensitivity assessment **is to be discussed in case by case** for each program starting its human development.

12° AT A GLANCE: PRO/CONS OF E14 PRIMARY ENDPOINT?

"BY TIME POINT" ANALYSIS

PRO

- Well known design
- Fewer model assumptions

CONS

- Late in the program
- Need for a dedicated study
- Expensive++
- Focus on a single time point (repeated)
- Sensitive to outliers (sponsor may be punished for adding one time point

EARLY QT PK/PD MODELING ("C-ER")

PRO

- Validated Alternative for QT waiver claim, as per the last ICH E14 Q&A (Dec2015)
- Logistically easy to implement
- Do not need to set an ECG specific study (cost!)
- Allows an ECG assessment on highest safely dosages (MTD)
- Could be performed afterward (post hoc analysis), if ECG trace has been recorded (12-leads Holter)
- Could facilitate the operations during the late stage program

CONS/"GREY ZONE"

- QT sensitivity assay is a "Nice to Have" (but not longer mandatory) for supporting a QT waiver request, but is not usually included during a SAD/MAD program
- Metabolite effect assessment (MAD)
- Acceptable C-ER modeling can be challenging
- High quality ECG collection (or 12-lead holter) during the FIM studies

Our opinion:

Always perform <u>at least</u> 12-lead holter recordings before and after dosing (steady state) during a MAD study, having in mind a subsequent "QT PK/PD modeling";

For facilitating a "QT waiver discussion" with regulatory bodies, consider (imagine) an "acceptable" QT assay sensitivity method.

THANK YOU …. Q&A

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For your agenda: Thursday April 21st, 2016 (05:30pm CET)

Free Banook webinar on early QT assessment

***with** T. Duvauchelle, M. Felices and P. Maison Blanche*

For registration, contact Alexandre Durand-Salmon (alexandre.durand-salmon@banookgroup.com)