EMA EFPIA workshop

Breakout Session 2

Assessing the Probability of Drug-Induced QTc-Interval Prolongation During Early Clinical Drug Development

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Background

- Drugs that prolong QT interval are associated with increased risk for ventricular arrhythmias (TdP) and sudden death

mean <5ms, **no risk** 5-20ms, **unclear risk** >20ms, **substantially increased risk**

- In almost all cases drugs should be thoroughly evaluated for possible effects on the QT interval in early clinical development.

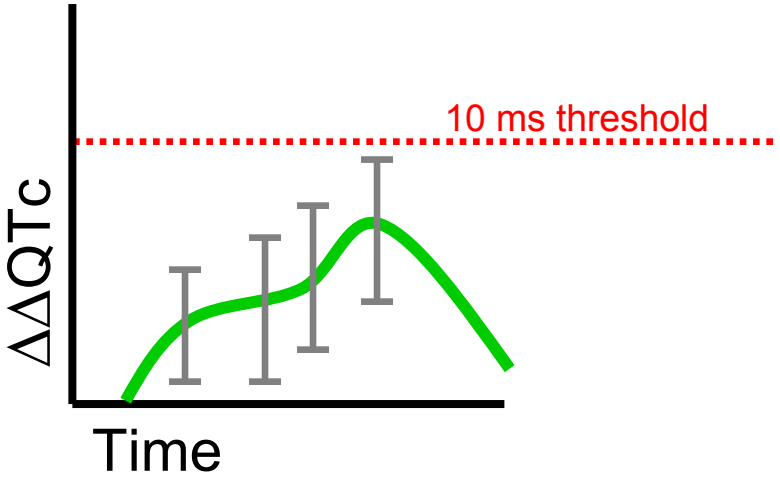
- A positive **thorough QT study** will almost always call for an extended ECG safety evaluation during later stages of development

ECG monitoring can account for up to 22% of Phase I costs.

Drug-induced prolongation of QT interval is #1 cause of approval delays and #2 cause of approved drug withdrawal

Background - TQT

- ICH E14 – recommends the double-delta methods for analysing and interpreting ECG findings
- Issues with double-delta method
  - Exposure information is not taken into consideration
  - Possible high false-positive rates

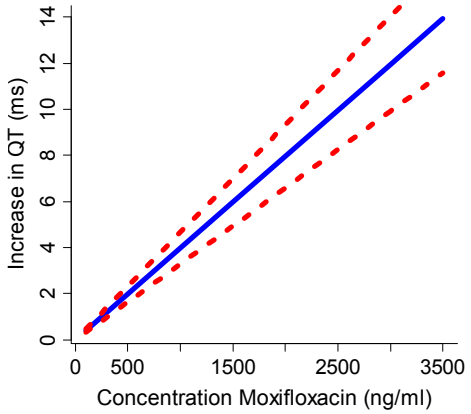


a negative TQT is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms

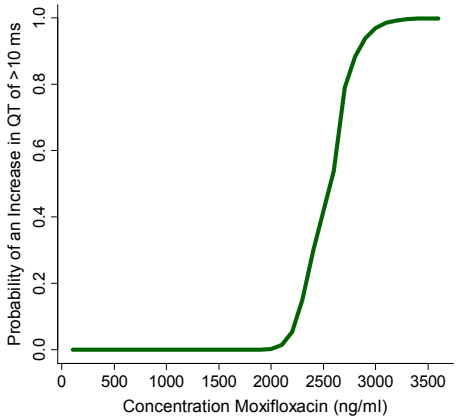
Modelling of QT interval prolongation

We propose the use of a parametric Bayesian approach to describe QT interval and assess the probability of prolongation during First-Time-in-Human trials

$$QT = \underbrace{QT_0 \cdot RR^{\alpha}}_{\text{individual heart rate correction}} + \underbrace{A \cdot \cos\left(\frac{2\pi}{24}(t-\phi)\right)}_{\text{circadian rhythm}} + \underbrace{slope \cdot C}_{\text{exposure-effect}}$$



- QT_0 is the intercept of the QT-RR relationship
  - Sex included as covariate
  - Inter-occasion variability
- α – individual heart rate correction factor (Fredericia α = 0.33, Bazett α = 0.5)
- C is the predicted concentration of drug at time of ECG measurement



FTIH Studies

- What is a FTIH study?
  - Phase I program during which PK, PD, safety and tolerability are evaluated
  - Traditionally small, dose escalated
  - Healthy volunteers or patients may be included
- Can modelling of FTIH study data provide evidence of a compound's liability for QTc interval prolongation?

FTIH – A Simulation Exercise

- Typical FTIH, n=6 per cohort

Subject	Day 1	Day 8	Day 15	Day 21	Day28
1	PLACEBO	D1	D2	D3	D4
2	D1	D2	PLACEBO	D3	D4
3	D1	PLACEBO	D2	D3	D4
4	D1	D2	D3	D4	PLACEBO
5	D1	D2	D3	PLACEBO	D4
6	D1	D2	PLACEBO	D3	D4

FTIH – A Simulation Exercise

- Modified FTIH, n=6 per cohort

Subject	Day 1	Day 8	Day 15	Day 21	Day28	Day 35
1	PLACEBO	D1	D2	D3	D4	MOXI
2	D1	D2	PLACEBO	D3	D4	MOXI
3	D1	PLACEBO	D2	D3	D4	MOXI
4	D1	D2	D3	D4	PLACEBO	MOXI
5	D1	D2	D3	PLACEBO	D4	MOXI
6	D1	D2	PLACEBO	D3	D4	MOXI

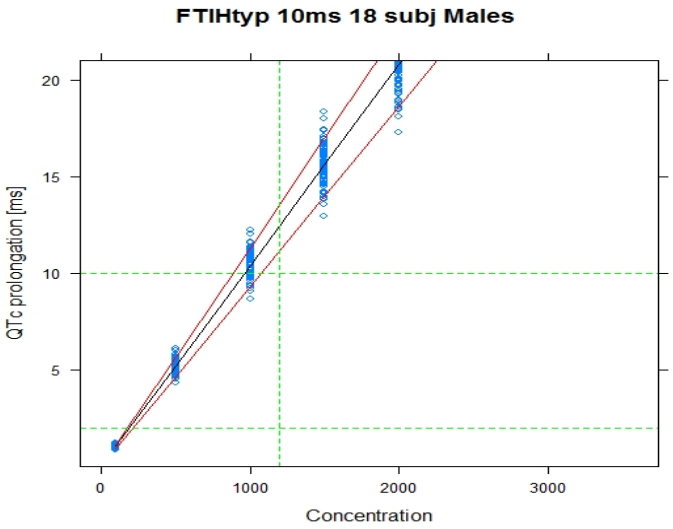
Comparison - protocol designs

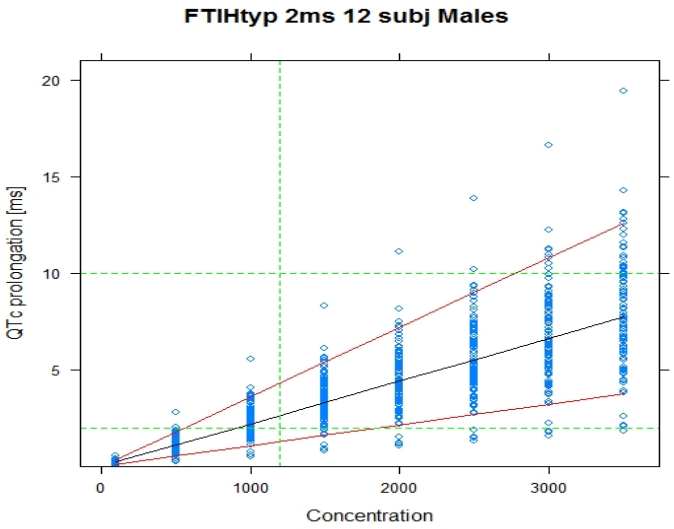
- TQT
  - 3 pre-dose baseline obs.
  - 13 post-dose obs.
  - Crossover, placebo controlled, single dose
  - N = 16, 30, 46, 60
  - Analysis method: double-delta
- FTIH
  - 3 pre-dose baseline obs.
  - 12 post-dose obs.

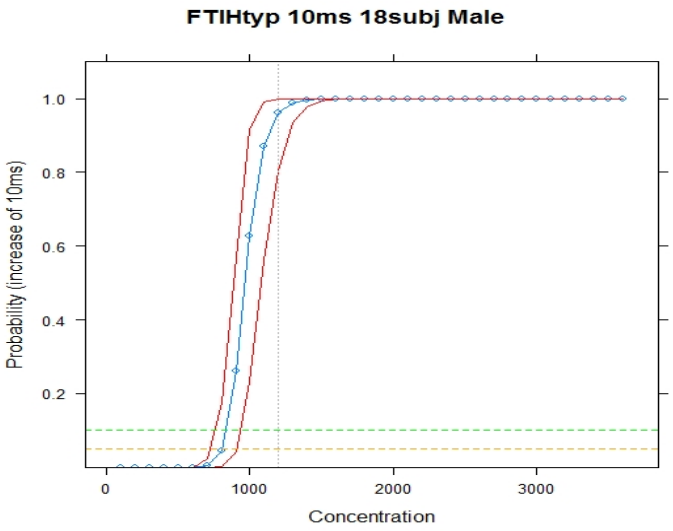
Sampling	Dose	Post-dose											
Time	0	0.5	1	1.5	2	2.5	3	4	6	8	12	18	24
PK		x	x	x	x	x	x	x	x	x	x	x	x
PD		x	x	x	x			x		x	x		x

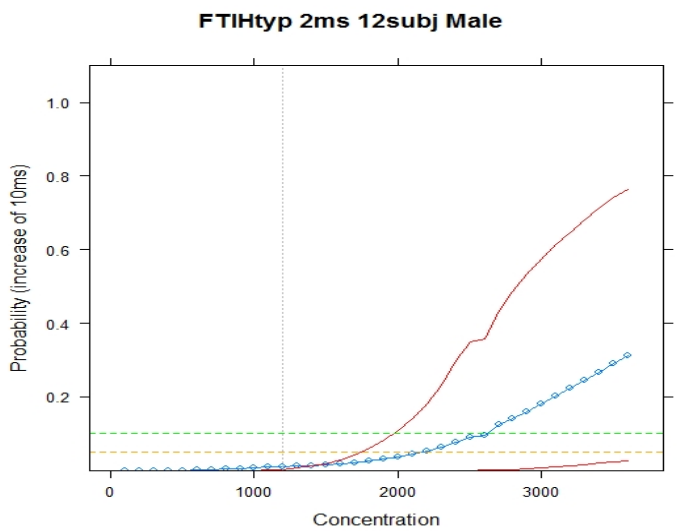
  - Crossover, placebo controlled, dose escalation
  - N = 12, 18, 27
  - Analysis method: Bayesian hierarchical model

M&S Results – FTIH typical design





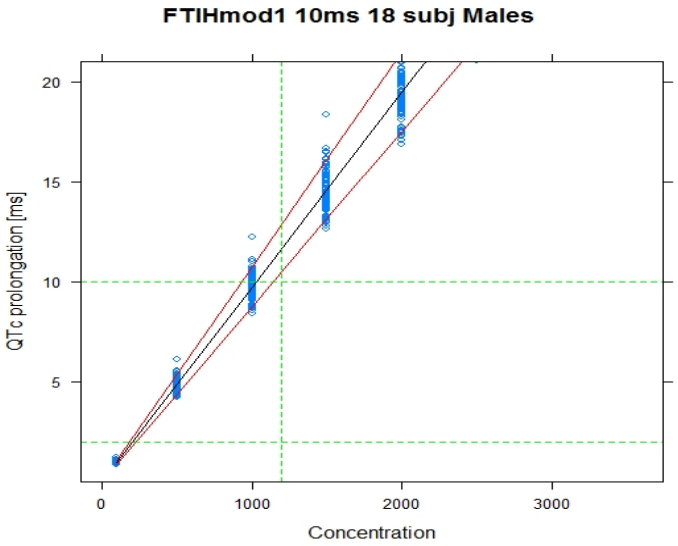


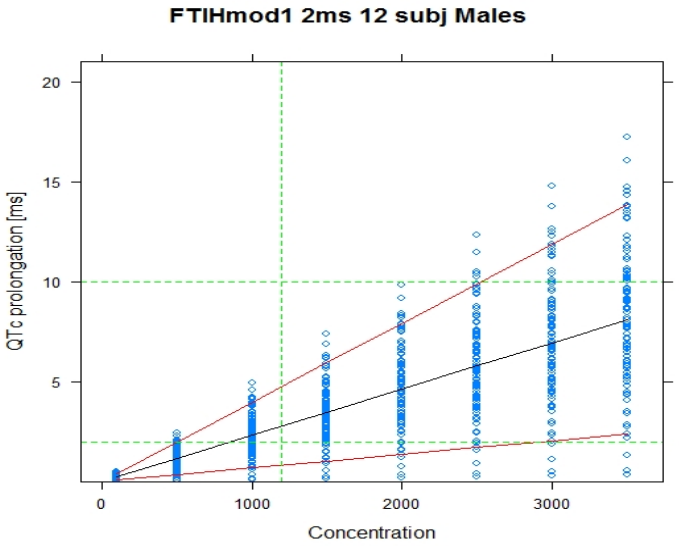


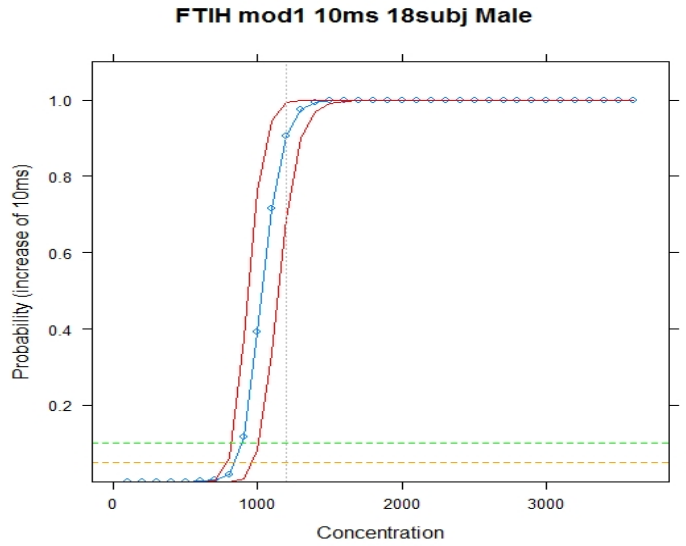
QT-prolonging drug

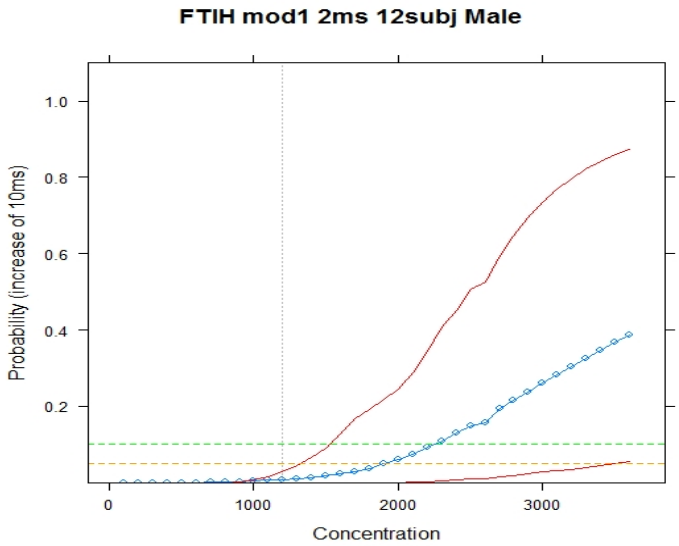
Negative control

M&S Results – FTIH + moxifloxacin PK priors









QT-prolonging drug

Negative control

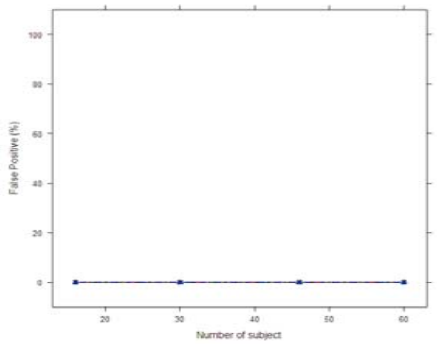
Sensibility/ Specificity

- TQT

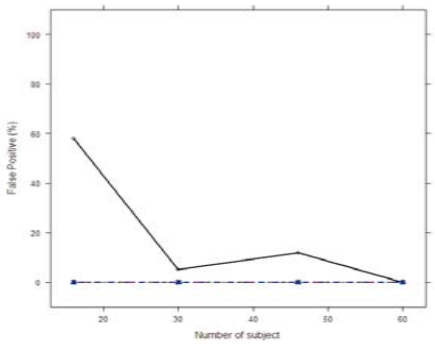
4 ms var on SLP		CRbl 16	CRbl 30	CRbl 46	CRbl 60
DD	Specificity	0,71	0,965	0,94	1
	Sensitivity	1	1	1	1
BUGS	Specificity	1	1	1	1
	Sensitivity	1	1	1	1

False positive rates

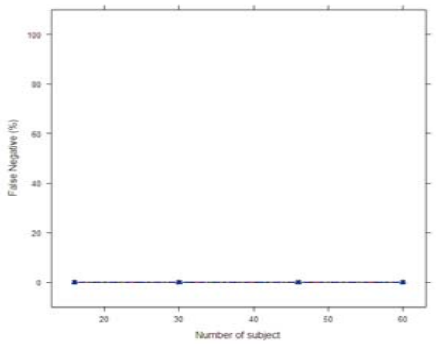
Crossover 2 ms



Crossover 5 ms



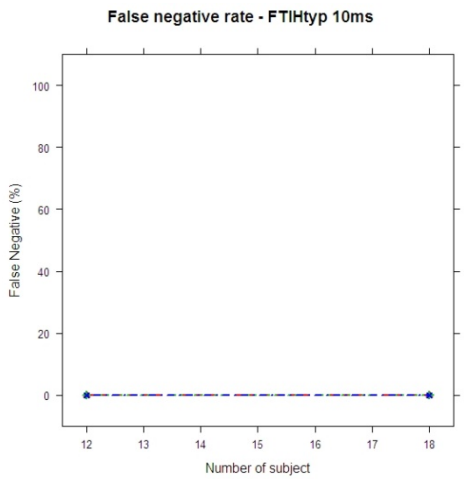
Crossover 10 ms

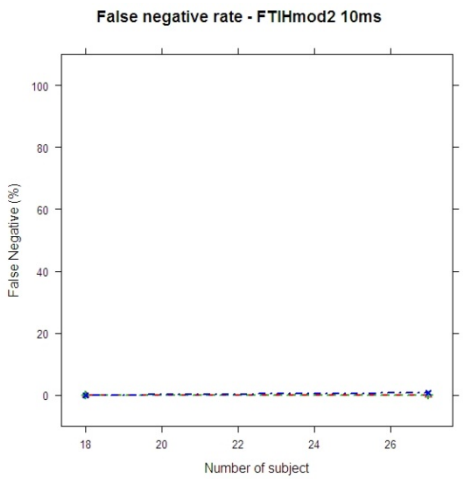


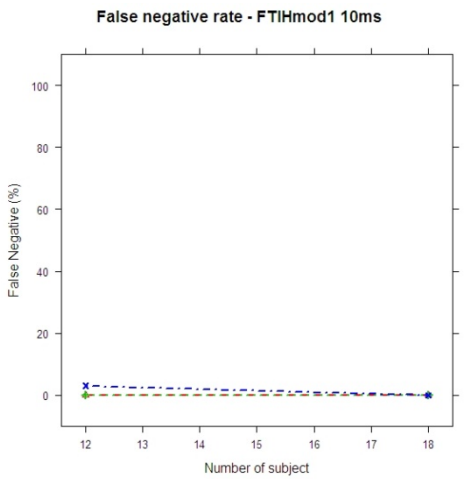
False Negative / False Positive Rates

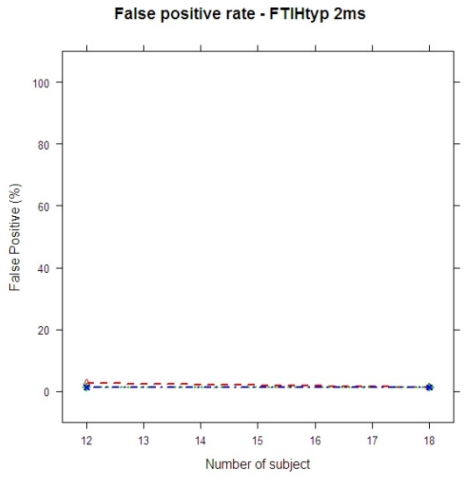
FTIH

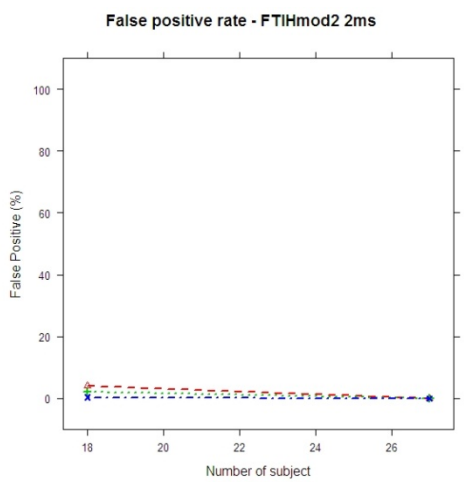
- Bayesian with P(10 ms inc)>99%
- Bayesian with P(10 ms inc)>95%
- Bayesian with P(10 ms inc)>90%

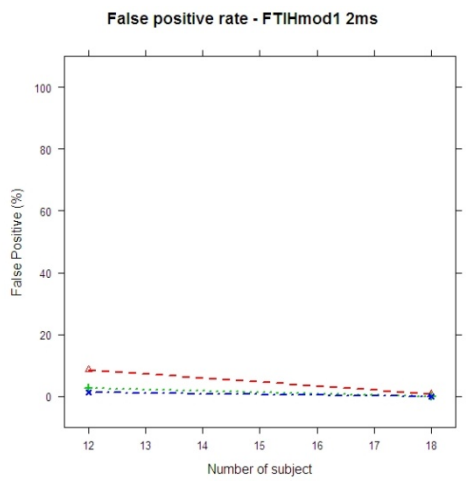












Conclusions

- The use of a Bayesian approach provides similarly **low rate of false negatives** compared to double-delta method
- The double-delta method shows an **unacceptably high rate of false positives** and is highly susceptible to the level of noise in the data
- The proposed PKPD modelling approach yields **a low rate of false positives and reliable estimates** of the drug effect on QTc interval, requiring as little as 12 subjects in a crossover study design.
- This **Bayesian analysis also facilitates the clinical interpretation of the risk associated with QTc interval prolongation**, which may help the decision process throughout the development of new compounds.

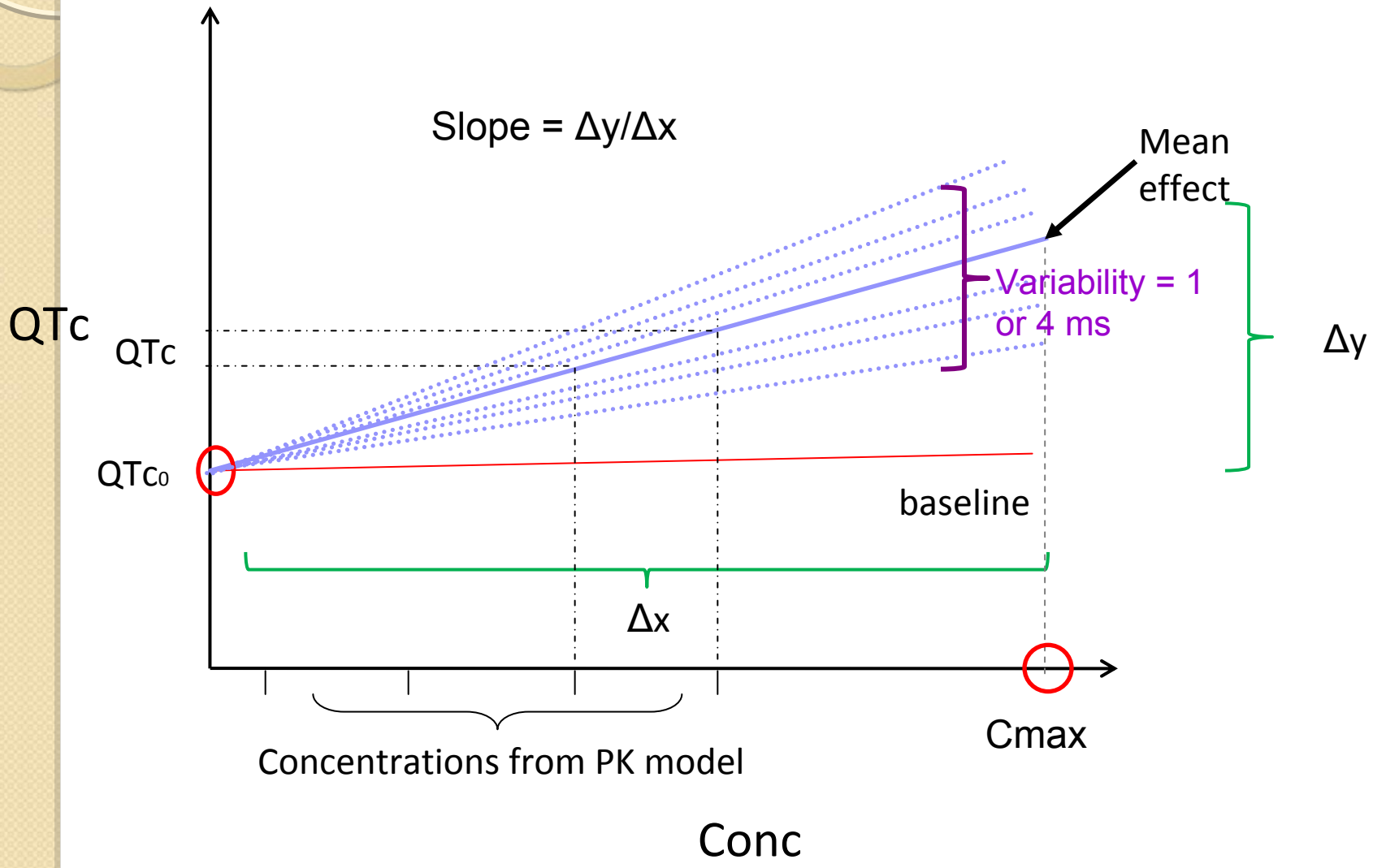
Backup slides

FTIH – A Simulation Exercise

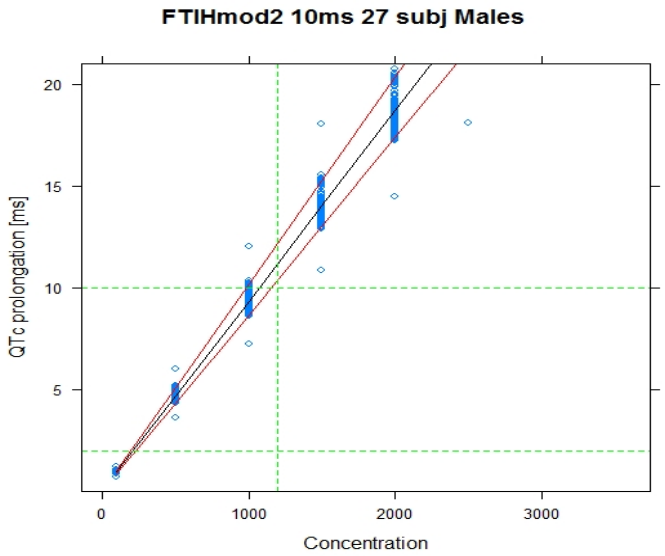
- Modified FTIH, n=9 per cohort

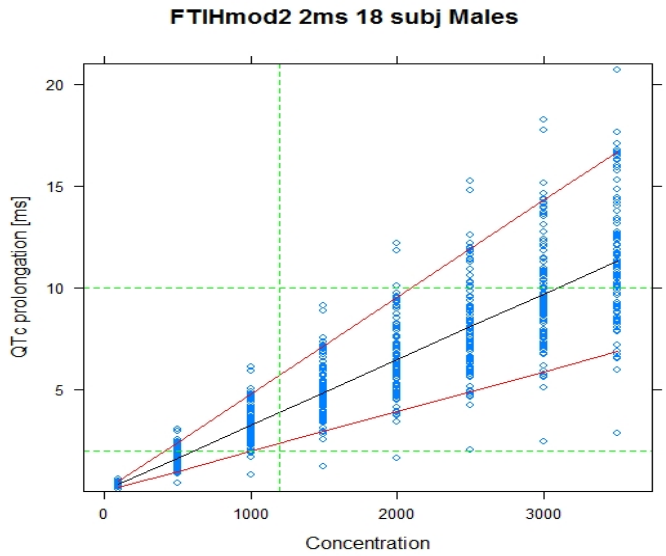
Subject	Day 1	Day 8	Day 15	Day 21	Day28	Day 35
1	PLACEBO	D1	D2	D3	D4	MOXI
2	D1	D2	PLACEBO	D3	D4	MOXI
3	D1	PLACEBO	D2	D3	D4	MOXI
4	D1	D2	D3	D4	PLACEBO	MOXI
5	D1	D2	D3	PLACEBO	D4	MOXI
6	D1	D2	PLACEBO	D3	D4	MOXI
7	PLACEBO	D1	D2	D3	D4	MOXI
8	D1	D2	D3	D4	PLACEBO	MOXI
9	D1	D2	PLACEBO	D3	D4	MOXI

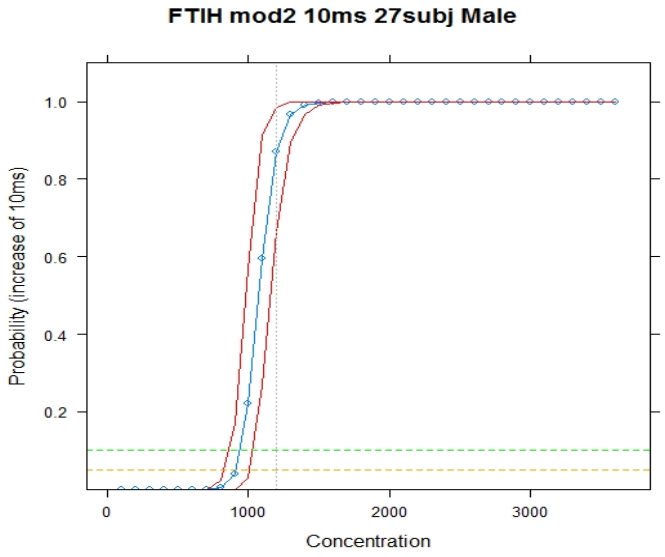
Simulation Method

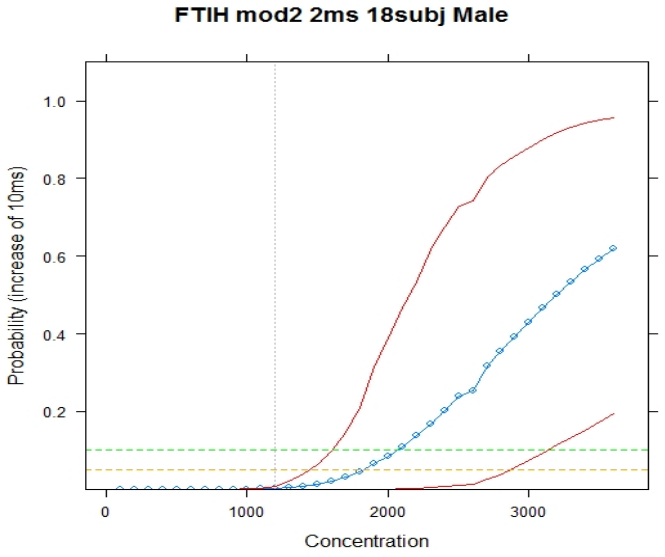


M&S Results – FTIH + moxifloxacin arm









QT-prolonging drug

Negative control

Definitions

$$\text{specificity} = \frac{\text{number of True Negatives}}{\text{number of True Negatives} + \text{number of False Positives}}$$

- Definition of false positive (drug effect = 2 or 5 ms): Double-delta or Bayesian analysis does detect ≥10 ms effect

$$\text{sensitivity} = \frac{\text{number of True Positives}}{\text{number of True Positives} + \text{number of False Negatives}}$$

- Definition of false negative (drug effect =10 ms): Double-delta or Bayesian analysis does not detect ≥10 ms effect

References

1. Chain, A.S.Y., Krudys, K., Danhof, M., Della Pasqua, O. Assessing the Probability of Drug-Induced QTc-Interval Prolongation During Clinical Drug Development. *Clin Pharmacol Ther* **90**, 867-875 (2011).

2. Anne Chain, Francesco Bellanti, Meindert Danhof, Oscar Della Pasqua. Can First-Time-In-Human Trials Replace Thorough QT Studies?, PAGE 20 (2011) Abstr 2172 [www.page-meeting.org/?abstract=2172]