Can First-Time-In-Human Trials Replace Thorough QT Studies?

Anne Chain[1], Francesco Bellanti[1], Meindert Danhof[1], Miriam Sturkenboom[2, 3], Oscar Della Pasqua[1,4]

[1]LACDR, Division of Pharmacology, Leiden University, Leiden, The Netherlands
[2]Department of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands,
[3]Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, The Netherlands
[4]Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park, United Kingdom

Introduction

The aim of thorough QT (TQT) studies is to determine if a new chemical entity (NCE) has the propensity to induce unintended QTc-interval prolongation. The requirements for the implementation and analysis of a TQT study are described in the ICH guideline E14. Recent data suggest that despite the expenditure of 2-7 million US dollars, conclusions about the magnitude of drug effects are possibly biased. In order to prevent unnecessary, cost-ineffective studies, it may be worth exploring how first-time-in-human (FTIH) trials can be used to evaluate the liability for QTc-interval prolongation. In the present study we investigate whether FTIH trials can be used to characterise the QTc-interval vs. concentration relationship and potentially eliminate the need for a TQT study.

Methods and Data

Three different FTIH trial scenarios with hypothetical drugs were evaluated using simulations in R2.12 and NONMEM VI. The hypothetical compounds were assumed to have no effect (2 msec), minor effect (5 msec) or significant effect (10 msec) on QTc-interval. Doses of 5, 10, 25, 50, 100, 250 and 500 mg of hypothetical compounds were given in all scenarios. Effects were considered detectable at doses of 150 mg and higher. Pharmacokinetic (PK) and pharmacodynamic (PD) sampling schemes were simulated according to standard FTIH protocols [*Table 3*]. Data analysis was performed in WinBUGS v 1.4.3, where the probabilities of QTc interval prolongation were derived from the underlying QTc-interval vs. concentration relationship[1].

Table 1

	Scenario 1 (Typical FTIH)	Scenario 2 (Modified 1 FTIH)	Scenario 3 (Modified 2 FTIH)
Trial Design	Five sessions, placebo-controlled trial with four consecutively escalating dose of hypothetical compounds.	Six sessions, placebo-controlled trial with five consecutively escalating dose of hypothetical compounds and a single dose of moxifloxacin as positive control.	Six sessions, placebo-controlled trial with five consecutively escalating dose of hypothetical compounds and a single dose of moxifloxacin as positive control.
Sample Size	A total of 12 subjects were simulated.	A total of 12 subjects (a) and 18 subjects (b) were simulated.	A total of 18 subjects (a) and 27 subjects (b) were simulated.
Randomisation	Subjects were divided into two cohorts. Cohort 1 received 5, 10, 25 and 50 mg of active drug and cohort 2 received 50, 100, 250 and 500 mg.	Subjects were divided into two cohorts. Cohort 1 received 5, 10, 25 and 50 mg of active drug and cohort 2 received 50, 100, 250 and 500 mg. All received moxifloxacin.	Subjects were divided into three cohorts. Cohort 1 received 5, 10, and 25 mg of active drug, cohort 2 received 25, 50, and 100 mg, and cohort 3 received 100, 250 and 500 mg. All received moxifloxacin.
Additional Information	Trial was analysed with uninformative prior (a) and historical moxifloxacin parameter estimates informative prior (b).	Only ECG measurements were taken when moxifloxacin was administered. Historical population PK values were used for both cohorts.	PK and ECG measurements were taken for all six sessions.

Table 1 – Trial design specifications are described for each of the different FTIH studies.

Tables 2a, b, c – Detailed randomisation scheme for each design: traditional FTIH (a), modified 1 FTIH (b), and modified 2 FTIH (c).

Table 3 – PK and PD sampling schemes commonly used in a standard FTIH protocol.

SUBJ	DAY 1	Day 8	DAY 15	DAY 21	DAY 28
1	PLA	D1	D2	D3	D4
2	D1	D2	PLA	D3	D4
3	D1	PLA	D2	D3	D4
4	D1	D2	D3	D4	PLA
5	D1	D2	D3	PLA	D4
6	D1	D2	PLA	D4	D4

Table 2a

SUBJ	DAY 1	Day 8	DAY 15	DAY 21	DAY 28	DAY 35
1	PLA	D1	D2	D3	D4	MOX
2	D1	D2	PLA	D3	D4	MOX
3	D1	PLA	D2	D3	D4	MOX
4	D1	D2	D3	D4	PLA	MOX
5	D1	D2	D3	PLA	D4	MOX
6	D1	D2	PLA	D4	D4	MOX

Table 2b

SUBJ	DAY 1	Day 8	DAY 15	DAY 21	DAY 28
1	PLA	D1	D2	D3	MOX
2	D1	D2	PLA	D3	MOX
3	D1	PLA	D2	D3	MOX
4	D1	D2	PLA	D3	MOX
5	D1	PLA	D2	D3	MOX
6	D1	D2	D3	PLA	MOX
7	PLA	D1	D2	D3	MOX
8	D1	D2	D3	PLA	MOX
9	D1	D2	PLA	D3	MOX

Table 2c

Sampling	Baseline				Dose	Post-dose											
Time	-1	-0.75	-0.5	-0.25	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	x	x	x	x
PD	x		x	x		x	x	x	x			x		x	x		x

Table 3

Results

It was possible to accurately predict the risk of 10 ms QT prolongation using FTIH data, with and without evidence from a positive control treatment arm. Figures 1, 2 3 represent a selection of the results. The variability in the relationship between QT prolongation and the probability of an increase ≥10 ms versus concentration was larger with smaller population size in all cases. The dotted vertical line in each of the graphs represent the concentration at which the hypothetical drug effects were confined to. The two dotted horizontal lines indicate the positive drug effect of 10 ms QT prolongation and negative effect of 2 ms increase. Each plot also contains the median, 5th and 95th percentile of the predicted QT prolongation as well as the probability of 10 ms increase.

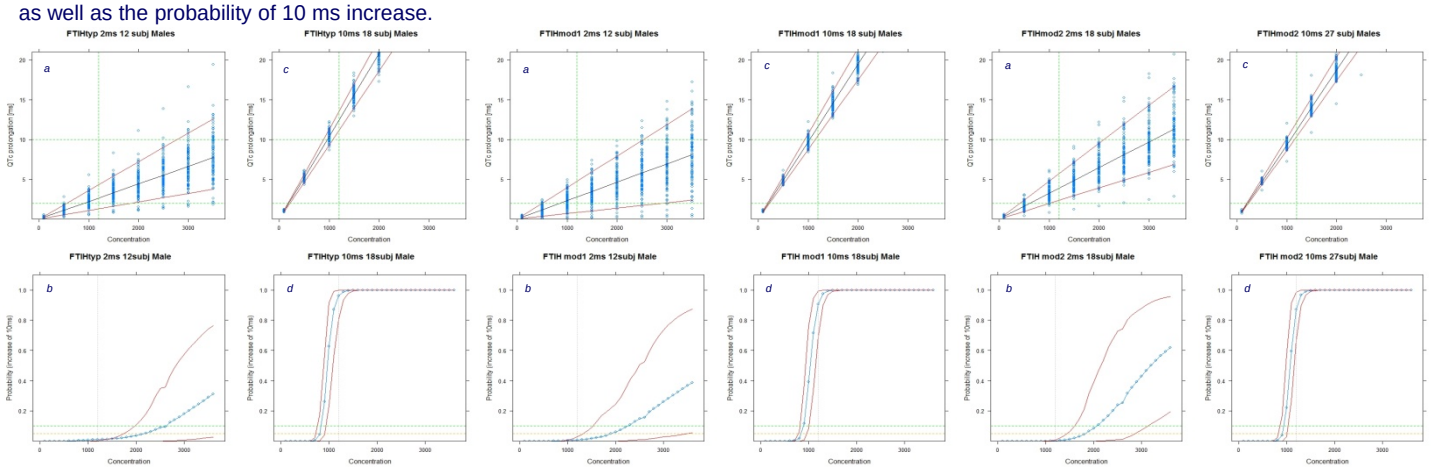

Fig 1 – Relationship between QT prolongation and probability of ≥10 ms increase vs. concentration for a negative compound with 12 subjects (a, b) and a positive compound in 18 subjects (c, d) using a typical FTIH trial design.

Fig 2 – Relationship between QT prolongation and probability of ≥10 ms increase vs. concentration for a negative compound with 12 subjects (a, b) and a positive compound in 18 subjects (c, d) using modified 1 FTIH trial design.

Fig 3 – Relationship between QT prolongation and probability of ≥10 ms increase vs. concentration for a negative compound with 18 subjects (a, b) and a positive compound in 27 subjects (c, d) using modified 2 FTIH trial design.

Conclusion

Concentration-effect relationships should be used as the basis for the assessment of the propensity for QTc-interval prolongation. Our results show that evidence for this relationship can be accurately derived from FTIH studies, making the need and relevance of a TQT study questionable.

[1] Krudys K., et al., PAGE 16 (2007) Abstr 1125 [www.page-meeting.org/?abstract=1125]

Leiden /Amsterdam Center for Drug Research

TI PHARMA

Erasmus MC Universitair Medisch Centrum Rotterdam