How can a small QT effect be excluded in early clinical trials with the same level of confidence as in the TQT study?

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Design considerations and measurement techniques in early studies.

Key factors – in my view

1. **Use more data, not less**
   a) Analysis based on concentration effect modeling results in greater power to exclude small effects the more data are used;
   b) To some extent, the power to exclude a small effect with the time matched analysis gets lower the more data (at least time points) are used.

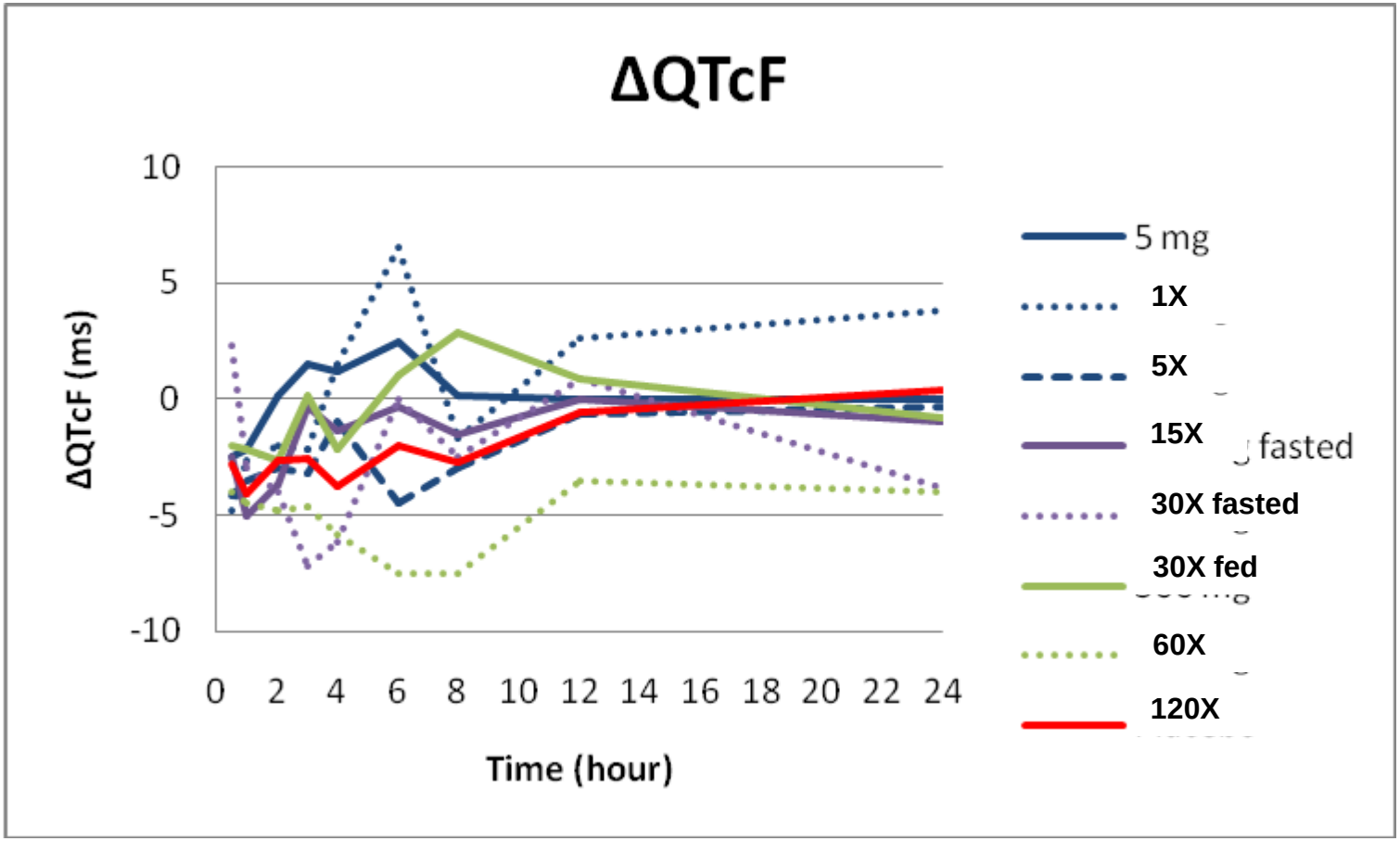
2. **Use more precise methodologies for QT measurement**

‘Enhanced’ QT assessment in early clinical studies

1. The objective of ‘enhanced’ QT assessment in early clinical trials can be to replace the TQT study
2. Should ideally not change the standard design of SAD/MAD studies
    a. There are many other, important objectives of these studies;
    b. Many projects are terminated for other reasons.
    c. TQT study in ‘surviving’ projects only.
3. Early studies provide a good opportunity to study QT effect at high plasma levels of the drug,
    1. But plasma levels in future patients are not well known

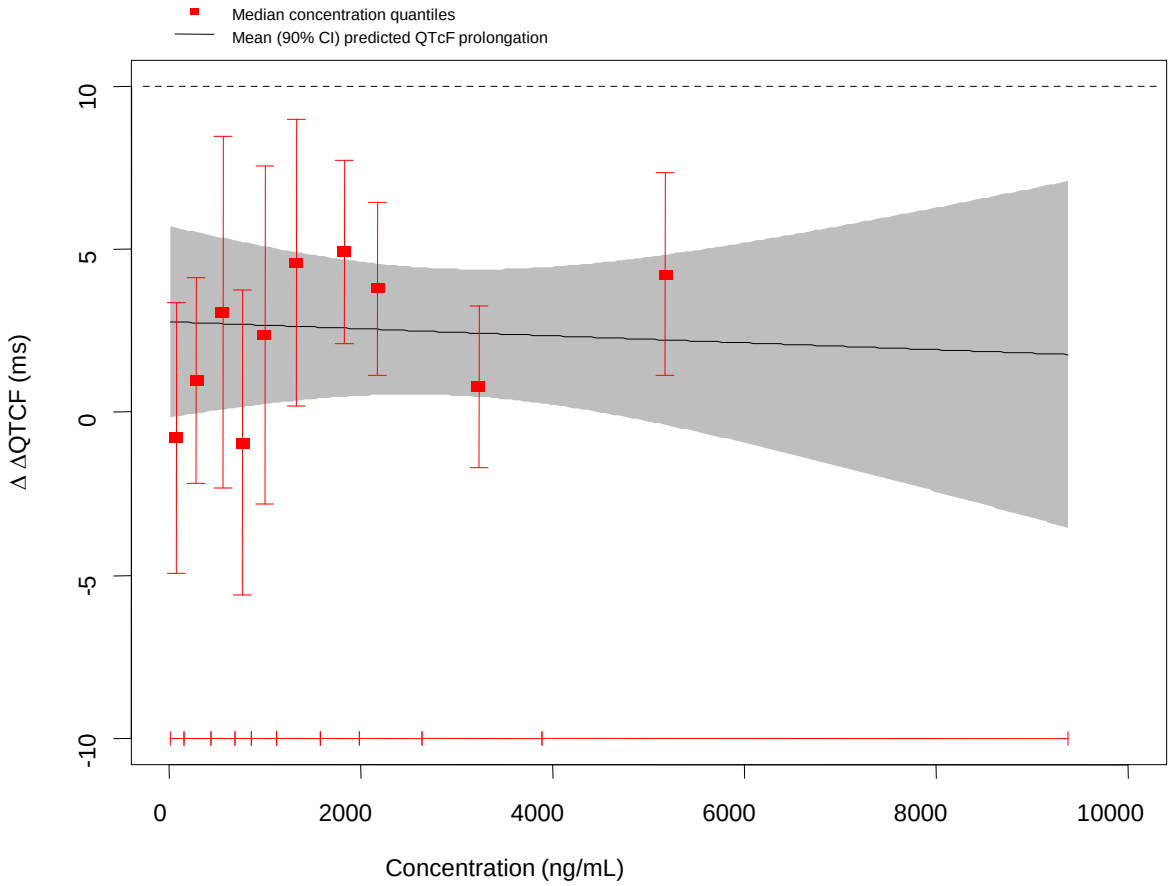
Results: SAD PART

12 ms ΔΔQTc effect could be excluded at high doses



Mean standard deviation of **ΔQTcF: 6 ms**

Concentration effect modeling of SAD/MAD data



Industry-Average Precision in TQT Studies Across Different Core Labs and CPUs

Study	N	Design	QTc	Mean DDQTc, ms	DDQTc CI, ms	Width of CI, ms	SD of DQTc, ms	Method
Morganroth, 2010	47	P	QTcF	9.6	3.3 to 15.9	12.6	18.4	SA
Moore, 2010	41	XO	QTcF	14.1	9.7 to 18.5	8.8	12	Manual
DeKam, 2010	82	XO	QTcI	20.8	UB 23.1	4.6	8.9	Manual
March, 2009	51	P	QTcI	9.4	UB 14.0	9.2	14	SA
Poordad, 2009	60	XO	QTcF	10	6.9 to 13.1	6.2	10.2	SA
Vande, 2009	73	XO	QTcF	10.3	7.8 to 12.7	4.9	8.9	Manual
Dalen, 2010	35	XO	QTcX	10	7.5 to 12.5	5.0	6.3	Eclysis*
Tyl, 2009	62	XO	QTcF	17.4	LB 13.5	7.8	13.1	Fully automated
	62	XO	QTcF	19.9	LB 16.9	6.0	10.1	SA1
	62	XO	QTcF	17.5	LB 14.7	5.6	9.4	SA2

CI: 90% confidence interval; P: Parallel; XO: crossover; QTcX: Study specific QTc correction; QTcI: Subject specific QTc correction; UB: Upper bound of 90% CI

***Note: Eclysis is a highly automated analysis method proprietary to AstraZeneca**

From Darpo et al. Improving the precision of QT measurements. Cardiology J 2011; 18: 401-10

CEM + high precision QT technique can provide >90% power to exclude a QT effect > 10 ms with small study sample sizes

Simulation using 2 moxi/placebo datasets

Fraction of negative studies

Effect	Analysis type	N=12	N=9	N=6
5 ms	TM	0.17	0.08	0.03
	CEM 1	0.72	0.60	0.41
	CEM 2	0.68	0.57	0.41
Insignificant	**TM**	0.63	0.42	0.20
	CEM 1	**0.96**	**0.89**	0.70
	CEM 2	**0.93**	**0.88**	0.78
None (placebo)	TM	0.78	0.58	0.31
	CEM 1	**1.00**	**0.97**	**0.88**
	CEM 2	**0.99**	**0.97**	**0.89**

Values in bold = more than 85% power to exclude an effect

Does the precision of the QTc measurement matter?

Sample size to provide 90% power to exclude a QTc effect > 10 ms using CEM
Parallel designed study

Underlying effect	SD of ΔQTcF	Number needed
3 ms	6 ms	9
3 ms	10 ms	21

Conclusions

- An analytical approach using concentration effect modeling and high precision QTc measurements
  - ✓ Can provide sufficiently high power to exclude small QTc effects using number of subjects that can be used in SAD/MAD studies
  - ✓ Better precision of the QT measurement substantially reduces the required sample sizes.