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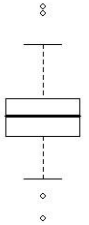

Data-based simulations to assess the power for detecting moxifloxacin-like QTc responses using concentration- QTc - models in small phase-1 studies

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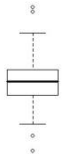
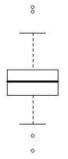
Motivation

- **ICH E14 defines 5 ms as threshold of regulatory concern.**
- **The threshold of 10 ms has been agreed upon for the E14 analysis based on the "largest time matched mean difference to placebo".**
- **In a phase I setting, this analysis lacks power and other methods such as a Concentration-Effect-Model based analysis (CEMA) may need to become primary.**
- **However, CEMA measures something different to E14.**
- **CEMA models need to be compared to the E14 analysis using signals that have known properties for the latter.**
- **To do so, we modified the response to moxifloxacin so that the maximum effect in an E14 analysis has a value of 5 or 10 ms.**



Outline of simulations

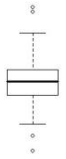
- **Use placebo and moxifloxacin data from TQT studies.**
- **Modify QTc response so that it has desired properties, but keeps the original correlation structure between timepoints and with concentration data.**
- **Simulate parallel group studies of various (small) sample sizes. Analyse using ICH E14 method and various variants of CEMA (1000 or 3000 resamples).**
- **Study the frequency of "negative" and "positive" studies.**
- **Study the frequency of studies meeting the FDA criterion for assay sensitivity (5 ms threshold) or its CEMA based analogue.**



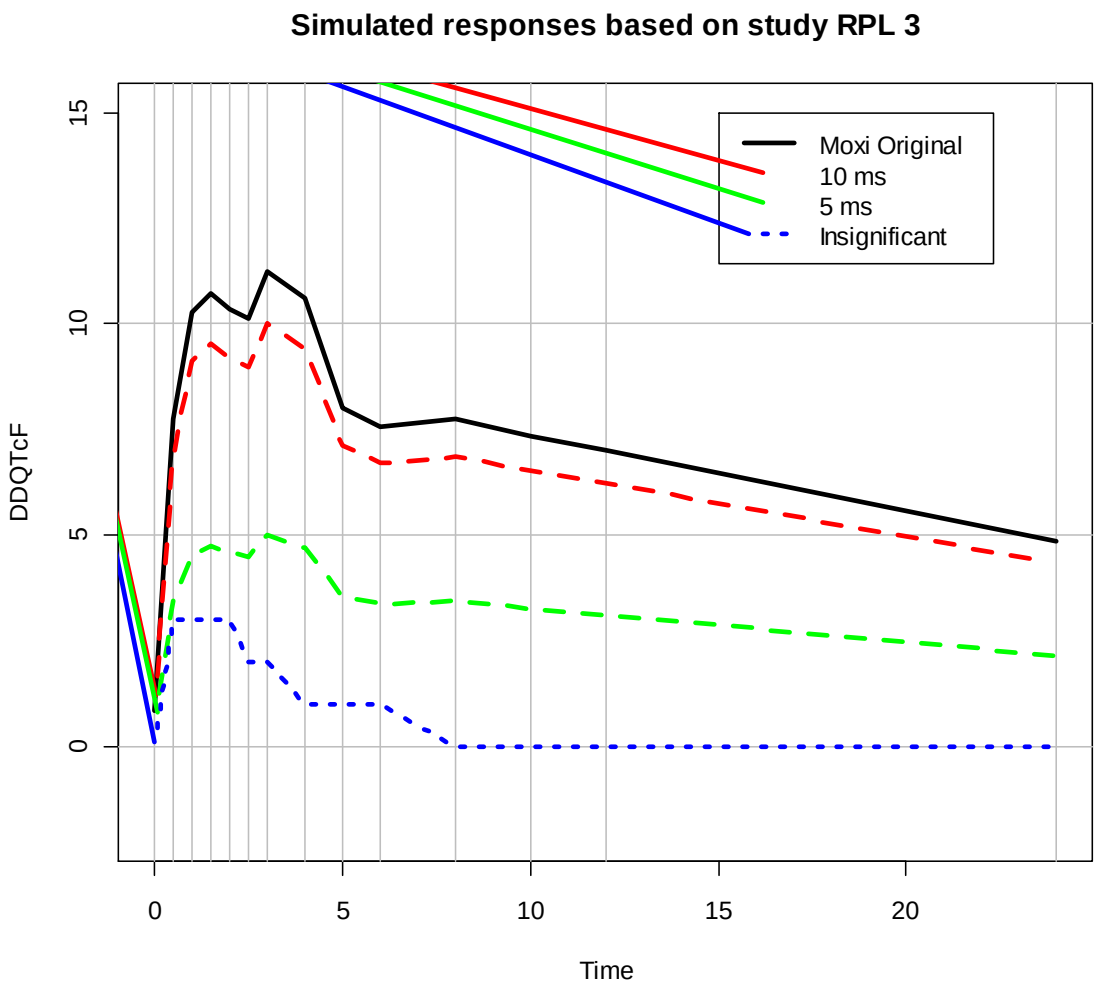
TQT studies used

5 crossover TQT studies:

- **iCardiac**
  (both studies have predose baseline and endpoint at day 1)
  - iC1: N = 29, 8 timepoints
  - iC2: N = 51, 9 timepoints
- **Richmond Pharmacology:**
  (all studies have full baseline day)
  - RPL1: N = 71, 12 timepoints
    endpoint at day 15
  - RPL2: N = 62, 12 timepoints,
    endpoint at day 1
  - RPL3: N = 48, 14 timepoints
    endpoint at day 1



Signals used



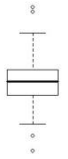
- **From individual moxi-responses**
  - subtract a fraction of the mean double difference to obtain a mean response of 5 or 10 ms.
- **To individual placebo data add**
  - nothing
  - a response up to 3 ms ("Insignificant").

CE model methodology

- **Fit mixed effects model with fixed and random intercept and slope**
- **Compute two sided 90 % confidence interval for prediction at**
  - upper 95 % CI of geometric mean C_{max}
  - lower 95 % CI of geometric mean C_{max} (for assay sensitivity)

(All computations based on resampled data only.)

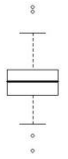
- **Compare upper limit to 10 ms**
- **Compare lower limit to 5 ms (assay sensitivity)**



What to expect?

- **Moxi and a maximum time matched difference of 10 ms should result in a positive study.**
- **Placebo and an "Insignificant" response should result in a negative study.**
- **Ideally true signals up to 5 ms should produce negative studies.**

- **Assay sensitivity should be shown with a 10 ms signal**
- **But should not be shown for a 5 ms signal.**



Results: Fraction of Negative Studies

Effect	Sample Size	CEMA	E 14
10 ms	12	**0.00** - 0.11	≤ **0.01**
	9	**0.01** - 0.09	≤ **0.01**
	6	**0.01** - 0.07	< **0.01**
5 ms	12	0.34 - 0.72	0.11 – 0.31
	9	0.30 - 0.60	0.06 – 0.17
	6	0.24 - 0.41	0.02 – 0.04
Insignif	12	**0.86 – 1.00**	0.40 – 0.87
	9	0.76 – 0.99	0.26 – 0.67
	6	0.63 – 0.93	0.10 – 0.29
Placebo	12	**0.96 - 1.00**	0.65 – 0.98
	9	**0.92 – 1.00**	0.43 – 0.87
	6	**0.81 – 1.00**	0.21 – 0.49

"Good" results in bold.

All but 1 study have values < 0.02 for all sample sizes

CEMA is by far more powerful than E 14

The results of 1 study with the 10 ms signal need further investigation.

Results: Fraction of Studies Showing Assay Sensitivity

Effect	Sample Size	CEMA	E 14 (FDA)
Moxifloxacin	12	**0.81 – 1.00**	0.31 – 0.92
	9	0.74 – 1.00	0.26 – 0.82
	6	0.66 – 0.98	0.17 – 0.63
10 ms	12	0.56 – 0.99	0.31 – 0.74
	9	0.47 – 0.98	0.26 – 0.59
	6	0.39 – 0.94	0.18 – 0.40
5 ms	12	0.07 – 0.46	**0.02 – 0.05**
	9	0.08 – 0.46	**0.02 – 0.05**
	6	0.09 – 0.40	**0.03** – 0.06

Only one study has false positive rates < 0.1 (for all sample sizes)

Discussion of CEMA Results

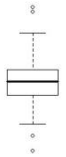
- **A moxi-like signal of 10 ms reliably leads to a positive study with sample sizes common in phase I studies (unlike with E14).**
- **With 12 subjects, placebo and signals up to 3 ms reliably lead to negative studies**

However:

CEMA-based analyses do not measure the maximum time matched difference to placebo:

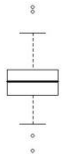
- **The Florian et al data show that the CEMA-based effect (evaluated at geometric mean C_{max}) is on average 1.4 ms smaller than in the E14 analysis.**
- **This is supported by the assay sensitivity results for 5 ms (which seem to be independent of sample size).**

Other simulated signals that take into account the concentration-response relationship do not give substantially different results.

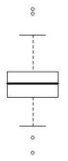


Conclusion

- **CEMA-based QTc-assessments in phase I studies are likely to provide a reliable signal for drugs that, based on an E14 analysis, have an effect of at least 10 ms.**
- **The E14 analysis has been conceived to catch many types of QTc-prolonging effects at the price of relatively low power – CEMA seems to be more powerful, but may not be as robust.**
- **E14 and CEMA do not measure the same quantity and a better understanding of the limitations of CEMA may be needed. Nonlinearity, hysteresis and other critical "perturbations" to the model need to be investigated.**

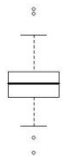


Thank you!



Results: Fraction of Negative Studies

Effect	Sample Size	iC 1	iC 2	RPL 1	RPL 2	RPL 3
10 ms	12	0.11	**0.04**	**0.03**	**0.00**	**0.01**
	9	0.09	**0.03**	**0.04**	**0.01**	**0.01**
	6	0.07	**0.04**	**0.04**	**0.01**	**0.01**
5 ms	12	0.72	0.68	0.34	0.59	0.63
	9	0.60	0.57	0.30	0.50	0.55
	6	0.41	0.41	0.24	0.38	0.40
Insignif	12	**0.96**	**0.93**	**0.86**	**0.94**	**1.00**
	9	**0.89**	**0.88**	0.76	**0.89**	**0.99**
	6	0.70	0.78	0.63	0.77	0.93
Placebo	12	**1.00**	**0.99**	**0.96**	**1.00**	**1.00**
	9	**0.97**	**0.97**	**0.92**	**0.98**	**1.00**
	6	**0.88**	**0.89**	**0.81**	**0.91**	**1.00**



Results: Assay sensitivity

Effect	Sample Size	iC 1	iC 2	RPL 1	RPL 2	RPL 3
Moxi	12	0.92	0.98	0.81	1.00	1.00
	9	0.82	0.95	0.74	0.98	1.00
	6	0.66	0.86	0.66	0.95	0.98
10 ms	12	0.56	0.88	0.81	0.99	0.99
	9	0.47	0.81	0.74	0.96	0.98
	6	0.39	0.71	0.66	0.93	0.94
5 ms	12	0.07	0.23	0.24	0.46	0.40
	9	0.08	0.25	0.23	0.46	0.37
	6	0.09	0.27	0.24	0.40	0.36