FDA Statistical Perspective on the Use of Concentration-QTc (C-QTc) Analysis in Assessing Drug Effect on QTc Intervals

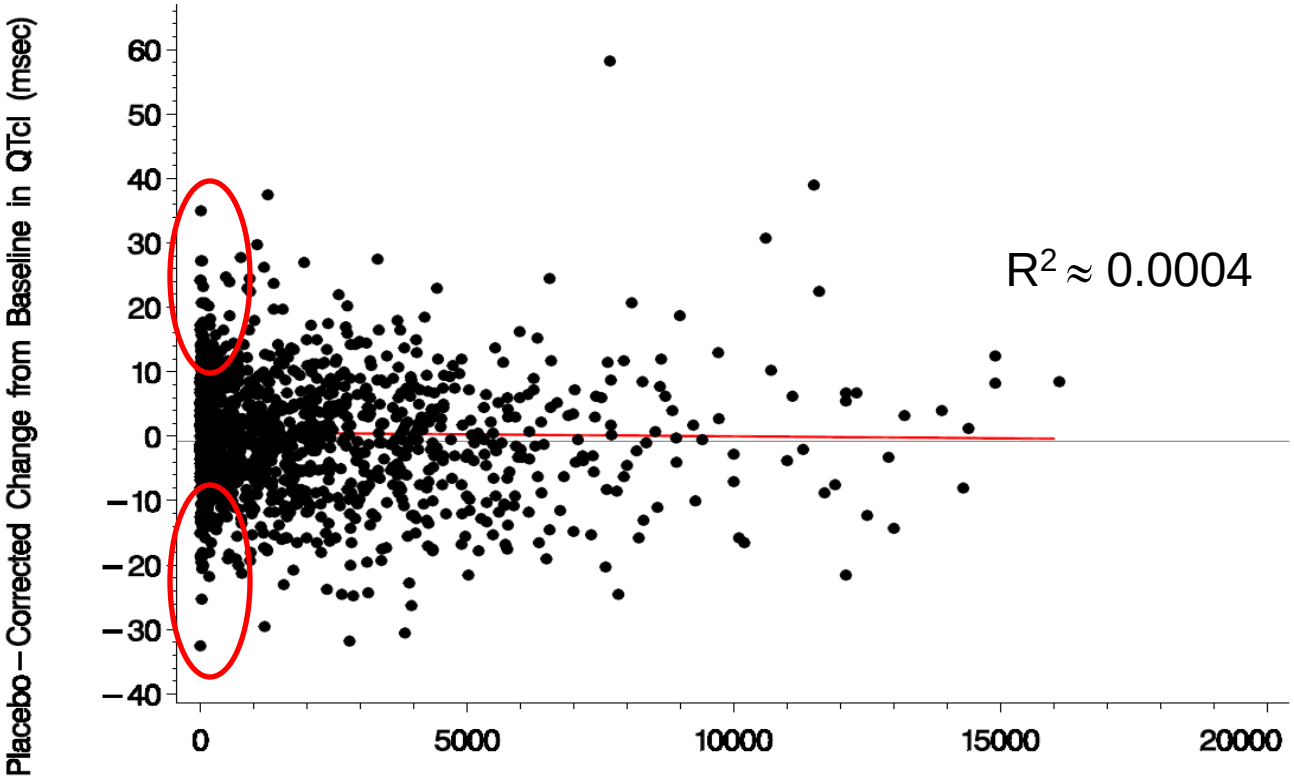
Presenter: Joanne Zhang, Ph.D.
Lead Statistician for QT-IRT
CSRC (2/2/2012)

C-QTc modeling – a useful tool

- C-QTc modeling can be used to demonstrate a strong signal of concentration-driven QTc prolongation
  - Make a go-no-go decision on the drug development or to waive a TQT study (a large positive slope if a linear or log-linear model considered).
- C-QTc modeling may also help
  - Select a dose (based on benefit-risk assessment).
  - Estimate QTc intervals at exposures not being studied.
- Assumptions:
  - The relationship between blood plasma concentration and QTc interval can be truthfully captured by the specified model.
  - The model is interpretable.

C-QTc modeling – a useful tool

- C-QTc modeling can also be used to test for the association between change of QTc and the concentration if the assumption of a linear relationship between the change of QTc and concentration is valid.



TQTS

- Well-controlled
- Randomized
- Appropriately blinded
- Placebo- and active-controlled
- Crossover or parallel study
- Objective: To demonstrate a lack of QTc effect near “worst case” scenario.

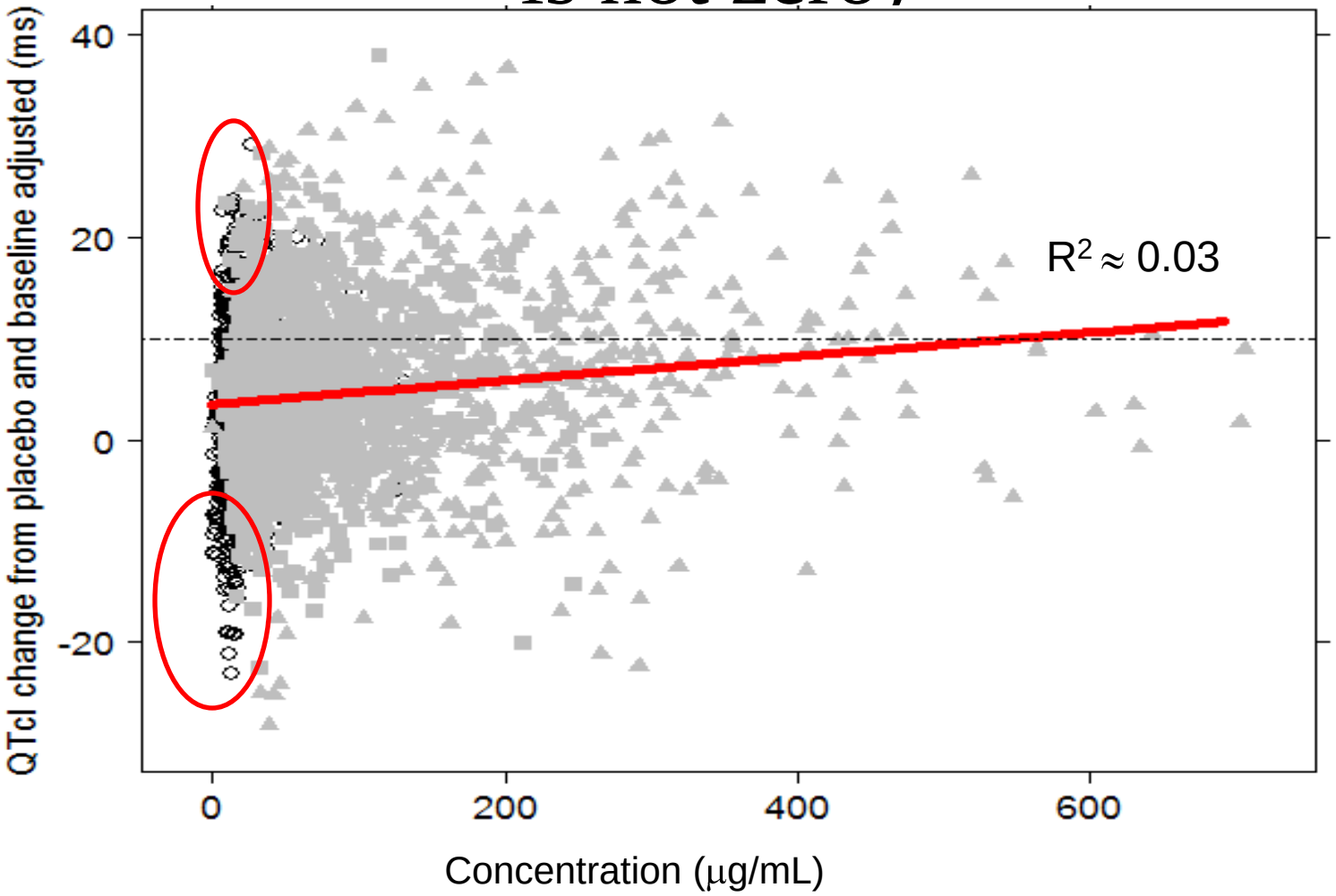
C-QTc: post-hoc approach

- Analyzing the data after the experiment is completed.
- "Technically, post-hoc analysis is any sort of analysis that occurs after you've looked at the data, literally post-hoc. When do you do it? I would say you always do it. When do you get it published and what do you do with it is the real question." – Professor Helena Kraemer from Stanford University.
- *"If only 1 or 2 of the ECG time points the 90% UB for ΔΔQTc is above 10 ms, then a determination of whether this is a false positive response will rely on the findings from the C-QTc model."* – *anonymous from sponsors*
  - C-QTc can not prove or disprove the findings of a pre-specified ICH E14 analysis.

C-QTc modeling

- Regress $\Delta\Delta$QTc against concentration. The most commonly used regression is a linear-linear or linear and log-linear regression with or w/o the intercept. Suppose $\Delta\Delta QTc=\beta*C+\varepsilon$.
- Then the worst $\Delta\Delta$QTc effect is approximately estimated as $\Delta\Delta QTc|_{\hat{\beta},\overline{C}_{max}}$ + margin error
- **Model**, **predict** the outcome based on a **fixed** number

ΔΔQTc versus concentration (when slope is not zero)



Using C-QTc model to predict the maximum QTc effect

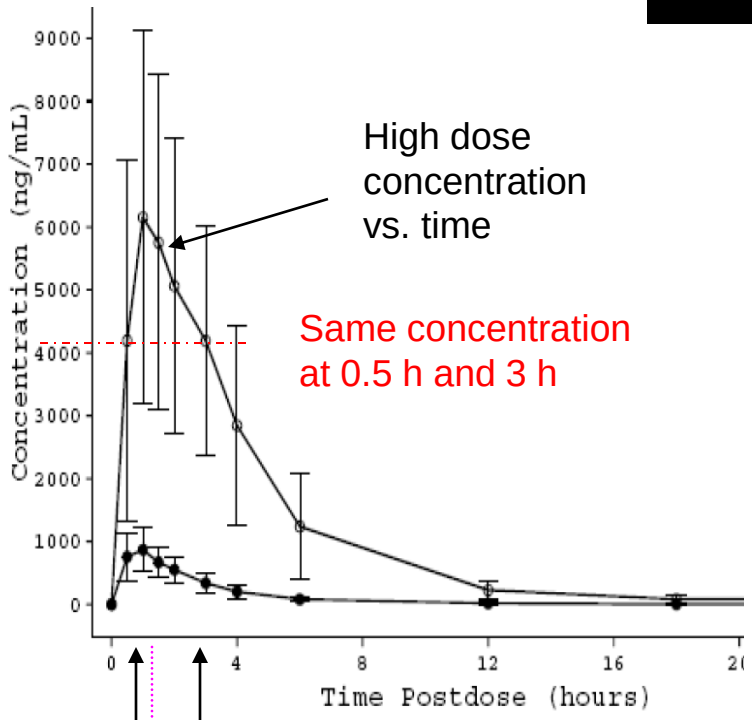
- How comfortable to use such a model to **predict** a mean response when the slope is not zero? (small R^2, lots of "outliers" near low concentration)
- Is it easy to identify a good model?
- $\overline{C}_{max}$ is treated as a fixed number, but it is a random variable with a considerably large dispersion.

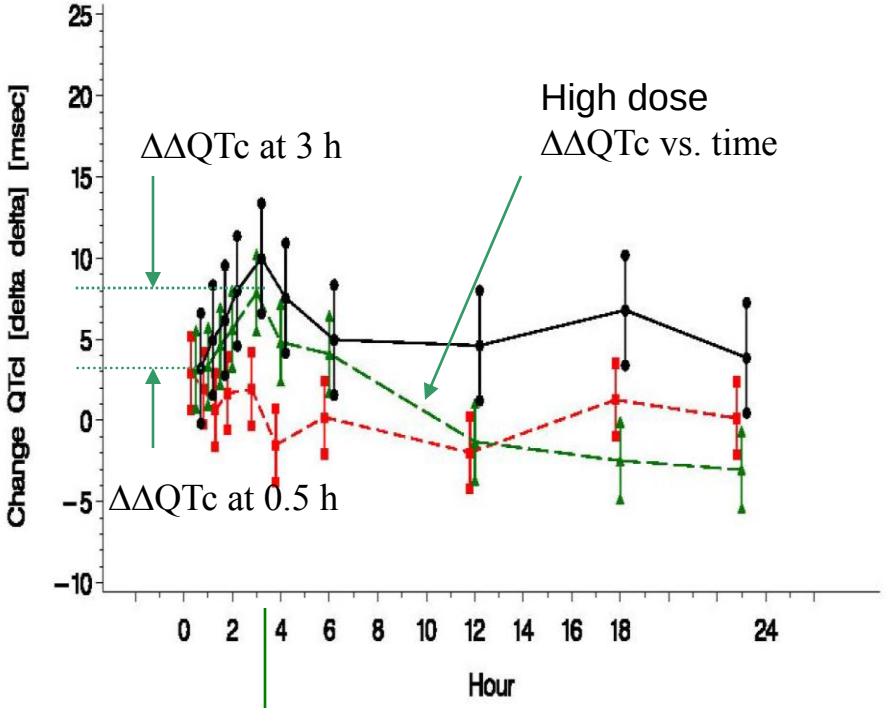
Coefficient variation (CV) for arithmetic/geometric $\overline{C}_{max}$

	Dosage (mg)	Arithmetic $\overline{C}_{max}$	**Arithmetic CV**	Geometric $\overline{C}_{max}$	**Geometric CV**
Study 1	50	42	**54%**	36.7	**59%**
	100	138.6	**43%**	124	**54%**
	200	329.5	**43%**	300	**48%**
Study 2	600	3966	**32%**	3787	**31%**
	2000	7923.1	**42%**	7278.6	**44%**
Study 3-group1	1950	67.3	**40%**	62.4	**42%**
Study 3-group2	1950	80.6	**31%**	77.1	**31%**

Relationship between ΔΔQTc and plasma concentration

ΔΔQTcI1≠ΔΔQTc2





Delayed PK-PD effect???

1 h: largest mean concentration

3 h: largest ΔΔQTc

Unable to incorporate the study design

- For a crossover study
  - $\Delta\Delta$QTc is calculated as a paired difference for each subject regardless of period/sequence.
- For a parallel study
  - $\Delta\Delta$QTc can not be constructed at individual level. Each subject shares a common single delta for the baseline adjusted placebo effect. For any subject i, $\Delta\Delta QTc(i)=\Delta QTc(i)$ (study drug) - $\overline{\Delta}$QTc (average baseline adjusted placebo effect)

    $\Delta QTc(i)$: single delta for the study drug

    $\overline{\Delta}QTc$: average baseline adjusted placebo effect (common for everyone)

    $\Delta\Delta QTc(i)$ (i=1,2,…,n) are not independent any more.
- The method can not take advantage of the study design.

Summary

In early stage (when SAD/MAD conducted)

- C-QTc can be used to demonstrate a large potential QTc effect
- C-QTc can be used to test if there is an association between QTc and concentration. If there is no association between the two, we probably don't have to worry about the potential drug-induced QTc effect. Having a wide range of doses is critical for this purpose.
- However, we are not ready yet to use C-QTc modeling to **predict** the outcome so that we can rule out a small QTc effect based on the following ICH E14 similar hypotheses

$$H_0: C_{max}\beta \geq 10 \text{ ms or } f(C_{max}, \beta) \geq 10 \text{ ms}$$
$$H_1: C_{max}\beta < 10 \text{ ms or } f(C_{max}, \beta) < 10 \text{ ms}$$

- Limitation of C-QTc modeling in TQTS:
  - Post-hoc analysis
  - Scatter plot shows a lot of large $\Delta\Delta$QTc values (positive or negative) at the lowest concentration level, which does not make physiological sense
  - Predict the worst drug-induced QTc effect based on a model built on a scatter plot described above, which has slight association between $\Delta\Delta$QTc and concentration ($R^2<0.1$)
  - No mathematic function exists (linear or nonlinear) if one concentration corresponds to two $\Delta\Delta$QTc
  - Statistical inference is wrong if the observed $\Delta\Delta$QTc(i) are not independent, which is the case in a parallel study
  - A possible delayed QTc effect will complicate the problem even more.

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