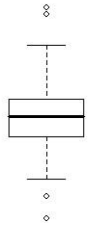
Presenting Results from the Prospective IQ-CSRC Clinical Study

Silver Spring MD, 2014-12-12



Statistical Considerations and Methods

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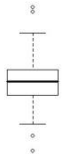
Overview

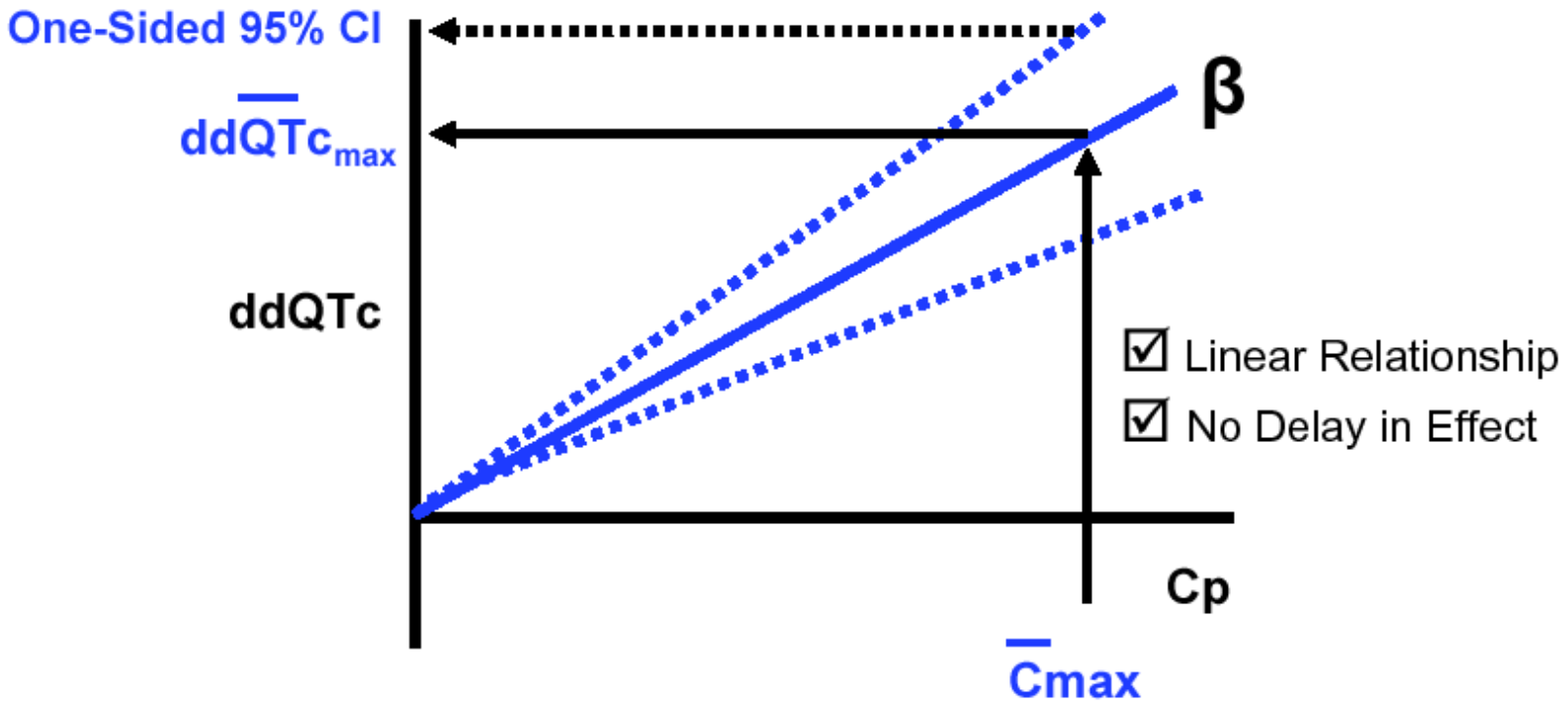
- **Concentration-response analysis has been around for quite some time**
- **It is the method of choice for Phase I (SAD, MAD) studies**
- **If used as primary analysis, it needs prospective planning**
- **What needs to be different in real Phase I studies?**



Concentration Response Analysis has been around for quite some time

$$H_0 : \overline{C}_{\max}\,\beta \geq 10\text{ms}$$

$$H_1 : \overline{C}_{\max}\,\beta < 10\text{ms}$$



from C. Garnett ca. 2006

There are various approaches

dQTc ~ treatment * time

Per time point analysis, one test per treatment and time point

ICH E14

ddQTc ~ C + intercept

Suitable for Crossover studies, one test.
A treatment effect has been added.

Garnett 2005

dQTc ~ C + time + trt

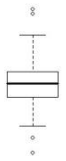
Time as factor replaces double difference.
Suitable for Parallel Group studies, one test.

Needleman and Garnett 2011

$$QT_c = QT_0 \cdot RR^{\alpha} + A \cdot \cos\left(\frac{2\pi}{24}(t-\phi)\right) + \text{Slope} \cdot C$$

More assumptions on circadian variability.

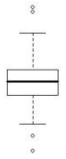
Chain et al 2011 (and others)



Prediction and test

Concentration-Response analysis allows the prediction at a chosen plasma concentration of the drug.

- **Case 1: Concentration is estimated from the study.**
  - Usually the geometric mean C_{max} is used
  - If a confidence interval is to be estimated for the prediction, the variability of C_{max} has to be taken into account
  - Bootstrap is the method of choice.
- **Case 2: Concentration has to be determined externally**
  - If the drug is known, may be predefined
  - For new drugs, a range of "safe" concentrations can be given
  - Prediction may need to be deferred to a later stage.



It is the method of choice for Phase I studies

Differences between TQT and Phase I studies

TQT Study	Phase I (SAD) Study
One or two doses of test drug	Many doses of test drug
Many subjects per dose	Few subjects per dose
Therapeutic dose known (?)	Therapeutic dose unknown

The prediction based on a concentration-response analysis can use all data across time points and dose groups.

- Its does not suffer from the problems of inverse multiplicity.
- It allows to defer the prediction of an effect under supratherapeutic doses to the time when these are known.

A considerable increase in power over the per time point analysis is to be expected.

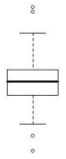
If used as primary analysis, needs prospective planning

Verify Assumptions

- **Absence of hysteresis**
- **Linearity of concentration-response relationship**

Models that do not need these assumptions can be used, but since they are more complex, they should only be used if indicated.

If CE-analysis is to be used as primary, tests that the assumptions are met need to be formalized.



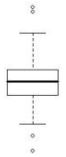
Absence of Hysteresis

There is some work on formal testing for hysteresis.

However, more research is needed to come up with criteria that can be used in practice.

We assume hysteresis when

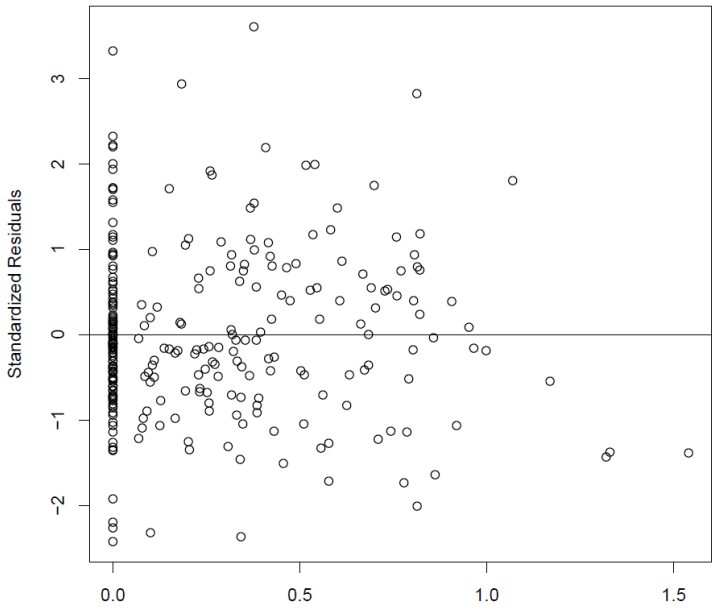
- **There is an effect on QTc**
  - at least 3 time points with $\Delta\Delta\mathrm{QTc} > 5\ \mathrm{ms}$
- **T_{max} and U_{max} (time of maximal effect on QTc) differ by > 1 h**
- **The values at U_{max} are "significantly" larger than those at T_{max}.**
  - A threshold for this (based on a formal Wilcoxon test) has been derived by simulation.



Linearity

In addition to an inspection of residual plots and normal QQ plots, a model with a quadratic term in concentration is fitted and the quadratic term tested on the two sided 10 % level.

Residual plot against concentration



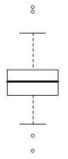
Reduce number of time points

There are 18 post dose time points

- **8 on Day 1,**
- **10 on Day 2 and 3.**

To reduce the number of nuisance parameters to be estimated, we

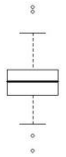
- **determined "significant time points" based on the data under placebo (6 subjects)**
- **used a model with "reduced time" in the primary analysis.**
  - "Reduced time" consists of the "significant" time points + one "other" time point only



Primary analysis

Fit model based on Day 1 and Day 2 data.

- **Model options chosen:**
  - dQTcF ~ Concentration + reduced time + treatment
  - Random effects: Intercept only
- **If hysteresis was present**
  - fit a model with an effect compartment, use primary model with the predicted concentration values from this effect compartment
- **If nonlinearity was detected**
  - fit at least a log-linear and an Emax model. Take the best fitting one as primary.



Primary outcome criteria

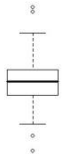
For positive drugs:

- **Significantly positive slope**
- **Upper limit of two-sided 90 % CI for predicted placebo-corrected dQTc at geometric mean C_{max} of Day 1 is above 10 ms**

For negative drug

- **Predicted placebo-corrected dQTc at geometric mean C_{max} of Day 2 significantly below 10 ms (i.e. upper limit of CI below 10 ms)**

Use bootstrap based CIs as primary



Sensitivity analyses performed

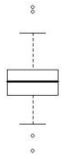
- **Model based on Day 1 data only (Day 2 for negative drug)**
- **Predictions at predefined concentrations**
- **Model with random slope included**

Post hoc:

- **Model excluding the active data for those subjects with two periods in the analysis – i.e. simulating a pure parallel group design.**

In addition:

- **Per time point analysis, summary statistics (HR, QT, QTcF, PR, QRS), categorical analysis and T/U wave morphology.**



What needs to be different in real Phase I studies?

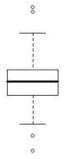
Our study mimics features of a SAD study, but it differs.

- **Only one cohort per drug**
- **Two doses in the same subjects.**

We somewhat mimic the high end of a SAD study.

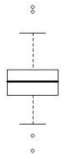
In a SAD study, we will have more subjects on higher and lower doses.

Our results therefore should be conservative.



Points to adapt

- **Prediction may need to be postponed until the therapeutic and tolerated supratherapeutic doses are known.**
  - Instead, a range of safe concentrations may be given.
- **If a subjects are re-used in several cohorts, the model may need to be adapted to reflect this.**
- **The test for hysteresis is based on simulations for our specific sample size. A more generally applicable procedure needs to be developed.**



Thank you.