A „thorough QT study“ in healthy volunteers

IBS/DR, GMDS, APF - Herbstworkshop 2005

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Thanks to Jürgen Lembcke and Stefanie Lindemann
A “thorough QT study”

A new ICH guideline

THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS

May 12, 2005

…but when planning our study, this guideline was only in draft status (2003).
**ICH E14 (final version)**  

**Design**

- adequate
- crossover has advantages
- randomized
- blinding
- placebo-controlled
- concurrent positive control (assay sensitivity)
- supratheurapeutic dose
- maximum metabolic inhibition
- „rechallenge“ in case of marked QTc prolongation or TdP (!)
- reduce variability (many ECGs; central reading; baseline days…)

A “thorough QT study”
A “thorough QT study”

QT “correction” (i.e., QT normalization)

- raw
- Bazett
- Fridericia
- linear regression
- non-linear regression for pooled databases
Analysis

- Analysis of central tendency (primary)

  A negative “thorough QT study” is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10msec.

- Categorical analyses

  Threshold analyses: QT(c) > 450 msec? 480 msec? 500 msec? Change from baseline > 30 msec? 60 msec?

- other

  Specific AEs, qualitative ECG wave characteristics, ...
“Largest time-matched mean effect”?

1) “Max change from baseline”:
   - Take "maximal change from baseline (over time, per subject and period)" as target variable.
   - Compare verum vs placebo.

2) Worst of all timepoints:
   - Separately for each time point, compare “change from baseline in verum” vs “change from baseline in placebo”.
   - Then take maximum over time points.

(2) is unfavorably biased!
The study

Our compound “ZK”

- Several indications
- Oral intake
- Targeted dose: possibly 600 mg
- Higher doses need ramp-up for better tolerability
- Intended for chronic use
- Slow and variable kinetics with double peak

- Show that on average, the administration of ZK does not prolong the QT(c) time to a clinically meaningful degree $\Delta$ [msec], compared to placebo

$\Delta = 7.5$? 5? 10? Two-sided? One-sided?
The study

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Design

Screening
N = 72

Randomization
6 male & 6 female
per sequence

<table>
<thead>
<tr>
<th>Sequ 1</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZK</td>
<td>Moxi</td>
<td>Pla</td>
<td></td>
</tr>
<tr>
<td>Sequ 2</td>
<td>Moxi</td>
<td>Pla</td>
<td>ZK</td>
</tr>
<tr>
<td>Sequ 3</td>
<td>Pla</td>
<td>ZK</td>
<td>Moxi</td>
</tr>
<tr>
<td>Sequ 4</td>
<td>Pla</td>
<td>Moxi</td>
<td>ZK</td>
</tr>
<tr>
<td>Sequ 5</td>
<td>Moxi</td>
<td>ZK</td>
<td>Pla</td>
</tr>
<tr>
<td>Sequ 6</td>
<td>ZK</td>
<td>Pla</td>
<td>Moxi</td>
</tr>
</tbody>
</table>

Follow-up

Administration within each period (double blind, double dummy):

<table>
<thead>
<tr>
<th>Day:</th>
<th>BL</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour:</td>
<td>0</td>
<td>1-8</td>
<td>8</td>
<td>16</td>
<td>0</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>ZK:</td>
<td>600 mg</td>
<td>600 mg</td>
<td>900 mg</td>
<td>900 mg</td>
<td>1200 mg</td>
<td>1200 mg</td>
<td>1200 mg</td>
</tr>
<tr>
<td>Moxi:</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
</tr>
<tr>
<td>Pla:</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
<td>ZK-Pla</td>
</tr>
</tbody>
</table>

Frequent ECGs on days BL, 1 and 3; 3 ECGs per time point; 5 beats per ECG

Frequent ECGs on days BL, 1 and 3; 3 ECGs per time point; 5 beats per ECG
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The study

Analysis

- **Primary target variable**
  - Maximum of time-matched QT(c) change from baseline
  - Maximum is taken over hours 1 to 8 at day 1 or day 3

- **Comparisons**
  - 600 mg ZK vs. placebo: Hour 1 to 8 on day 1; CI below 7.5 / 5 msec?
  - 1200 mg ZK vs. placebo: dito on day 3.
  - Moxifloxacin vs. placebo (assay sensitivity): Hour 1 to 8 on day 3; CI above 0?

- **Model**
  - Mixed model ANOVA, separately for day 1 and day 3
  - fixed factors "sequence", "period" and "treatment"
  - random factor "subject" nested in sequence
  - baseline value (at the hour of the max change) as continuous covariate

- …plus: mean of time-matched ctb; per-timepoint-analysis; at \( t_{\text{max}} \); etc
The study

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Analysis (cont.) - QT corrections

- Raw; Bazett; Fridericia
- 3 regressions (linear, log, exp; based on drugfree data)
- each regression in 3 versions (individual, per gender, pooled)
- each correction in 2 variations (per beat, per ECG)
The study

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Results – primary analysis

Maximum of time-matched QTc change from baseline within the first 8 hours after administration; QT correction per ECG: Fridericia

<table>
<thead>
<tr>
<th>Day</th>
<th>Comparison</th>
<th>Active dose</th>
<th>Estimate [msec]</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZK - Placebo</td>
<td>600 mg</td>
<td>2.93</td>
<td>1.00</td>
<td>4.86</td>
</tr>
<tr>
<td>3</td>
<td>ZK - Placebo</td>
<td>1200 mg</td>
<td>6.24</td>
<td>3.80</td>
<td>8.68</td>
</tr>
<tr>
<td>3</td>
<td>Moxifloxacin - Placebo</td>
<td>400 mg</td>
<td>10.26</td>
<td>7.83</td>
<td>12.70</td>
</tr>
</tbody>
</table>

➢ Conclusion:

QTc prolongation by low dose less than 5msec. High dose failed.
Assay sensitivity established.

…but note: in the final E14, the upper bound for the one-sided 95% CI is 10 msec.)
**The study**

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### Results (cont.) - per-timepoint-analysis on day 1:

Time-matched QTc change from baseline per hour; QT correction per ECG: Fridericia

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Day</th>
<th>Hour</th>
<th>Estimate</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZK - PL</td>
<td>1</td>
<td>1</td>
<td>-0.86</td>
<td>-3.10</td>
<td>1.38</td>
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<tr>
<td></td>
<td>2</td>
<td>0.22</td>
<td>-2.00</td>
<td>2.45</td>
<td></td>
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<tr>
<td></td>
<td>3</td>
<td>2.73</td>
<td>0.54</td>
<td>4.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.65</td>
<td>0.51</td>
<td>4.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.72</td>
<td>0.20</td>
<td>5.24</td>
<td></td>
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<tr>
<td></td>
<td>6</td>
<td>2.90</td>
<td>0.69</td>
<td>5.11</td>
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<tr>
<td></td>
<td>7</td>
<td>1.93</td>
<td>-0.37</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.73</td>
<td>-0.38</td>
<td>3.83</td>
<td></td>
</tr>
</tbody>
</table>
The study

Results (cont.) - different QT corrections and target variables

- **Bazett**
  
  Same conclusions, except: 600 mg ZK - placebo smaller than 7,5 msec

- **corrections per beat**
  
  maximal difference to correction per ECG: 0,15 msec (Bazett MX-PL)

- **other QT correction methods**
  
  - very small differences between different regression based corrections
  - regression based corrections ≈ Fridericia

- **categorical analyses and outlyers**
  
  - only Moxifloxacin vs Placebo shows an effect
  - no differences in ECG wave characteristics
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Conclusions

- **About the compound:**
  - 600 mg SD: quite safe
  - 1200 mg MD: borderline

- **About ways of QT analysis (if I dare generalize...):**
  - Think about your endpoint. (Update E14?)
  - QT correction per ECG is sufficient.
  - Use Fridericia for simplicity and comparability (often used, quite OK).
  - Do a regression. Population-based linear regression is OK.
  - Don't do much more.
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Thank you!
Appendix

Regression-based QT correction

- **linear**

\[ QT = \alpha + \beta RR \]

\[ QT_{RR=1} = \alpha + \beta = QT - \beta RR + \beta = QT + \beta (1 - RR) \]

- **Linear on the logscale**

\[ QT = \alpha \ RR^\beta \]

\[ QT_{RR=1} = \alpha = QT / RR^\beta \]