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The Relationship between Pharmacokinetic exposure and QT prolongation in Cardiac Safety Trials

A Ring (Phase I-IIa Biostatistics)
Boehringer Ingelheim Pharma GmbH & Co. KG

Overview

- The QT interval as a biomarker
- Primary analysis according to ICH E14
- “PK-QT modelling” analysis in TQT studies
 - Linear and nonlinear approach
 - Case studies
 - Current regulatory position
- Use of exposure response-modelling
 - Early Phase I studies
 - Oncology
- Conclusions

The QT interval as a biomarker

ICH E14

- “A feature of TdP is pronounced prolongation of the QT interval in the supraventricular beat preceding the arrhythmia. TdP can degenerate into ventricular fibrillation, leading to sudden death.
- While the degree of QT prolongation is recognized as an **imperfect biomarker** for proarrhythmic risk, in general there is a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT interval.”

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The QT interval as a biomarker

A possible study design for a biomarker (one study period)

- Baseline Day
 - Measurement of biomarker
 - **Non-pharmacological intervention**
 - Repeated measurements of biomarker over the day
- Treatment day
 - Measurement of biomarker
 - **Treatment**
 - **Non-pharmacological intervention**
 - Repeated measurements of biomarker and PK over the day



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The QT interval as a biomarker

A possible study design for GLUCOSE in metabolic trials

- Baseline Day
 - Measurement of glucose
 - **Glucose/Meal tolerance test**
 - Repeated measurements of glucose over the day
- Treatment day
 - Measurement of biomarker
 - **Treatment**
 - **Glucose/Meal tolerance test**
 - Repeated measurements of glucose and PK over the day



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The QT interval as a biomarker

A possible study design for QT studies

- Baseline Day
 - ECG recording
 - **Avoid any interventions/stress**
 - Repeated ECG recordings over the day
- Treatment day
 - ECG recording
 - **Treatment**
 - **Avoid any interventions/stress**
 - Repeated ECG recordings and PK measurements over the day



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The QT interval as a biomarker

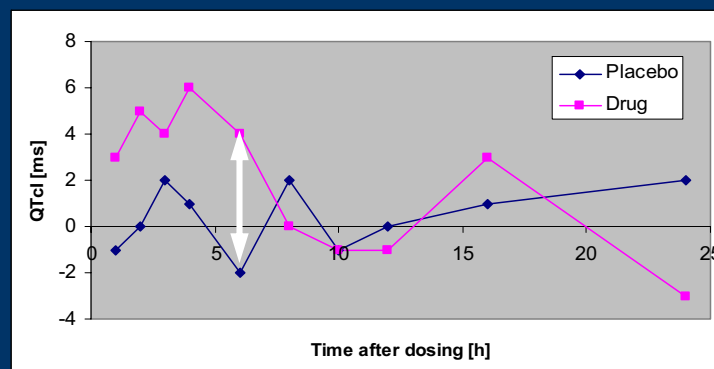
Reasons for such study designs

- Allow for intraindividual comparison of baseline and treatment data
 - Cover circadian rhythms or other systematic patterns of the biomarker
- Pharmacokinetic measurements are sampled together with biomarker measurements to **enable integrated exposure-response modelling**
- The QT interval can be interpreted as “just another biomarker”, and hence similar methods as for other biomarkers could be utilized

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E14: Largest mean effect over time

- Taking the treatment mean at each time point
- Difference 'active to placebo'
- **Largest** difference over time



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Primary analysis according to ICH E14

- Primary analysis in “thorough QT studies” is only based on the ECG recordings
- Pharmacokinetic measurements were primarily seen to justify the appropriateness of the trial design, specifically the selection of the doses and of the sampling times
- “While the peak serum concentration does not always correspond to the peak effect on QT/QTc interval, care should be taken to **perform ECG recordings at time points around the C_{max}**.”
- “In general, the duration of dosing or dosing regimen should be sufficient to characterize the effects of the drug and its active metabolites at **relevant concentrations**.”
- “If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at **substantial multiples** of the anticipated **maximum therapeutic exposure**.”

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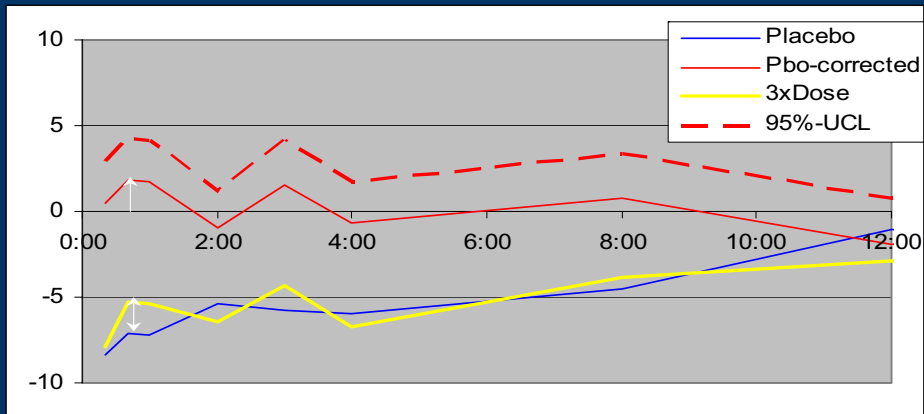
Primary analysis according to ICH E14

- Reasons for this specification of this primary analysis
 - This primary analysis is in most cases conservative and hence provides efficient protection of the public
 - Analysis is rather easy to describe (but statistically it is not so easy to implement it)
- Main difference: QT (c) interval is a safety parameter
 - Analysis should not be based on modelling assumptions which could potentially be wrong
 - For regulators, safety biomarkers are of more importance than efficacy biomarkers

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E14: Largest mean effect over time

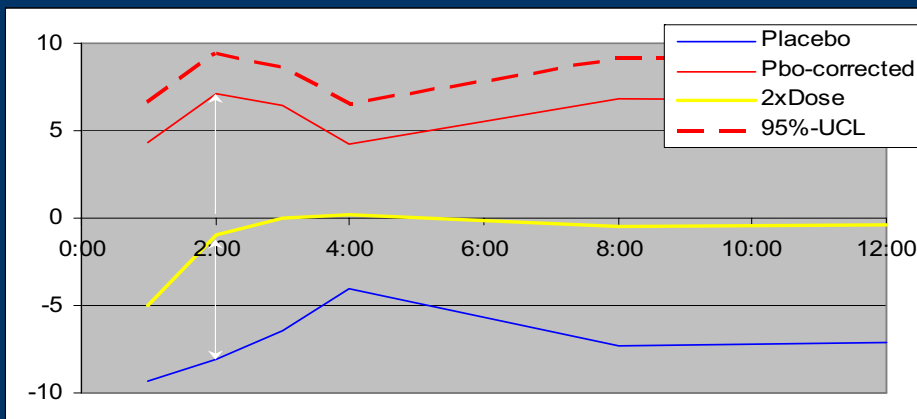
- Case study **A** for “no effect drug”
- QTcN time-matched change from baseline
- Largest difference: 1.8 ms (with 4.3 ms 95% UCL)
- Note the placebo effect for the change from baseline (day -1)



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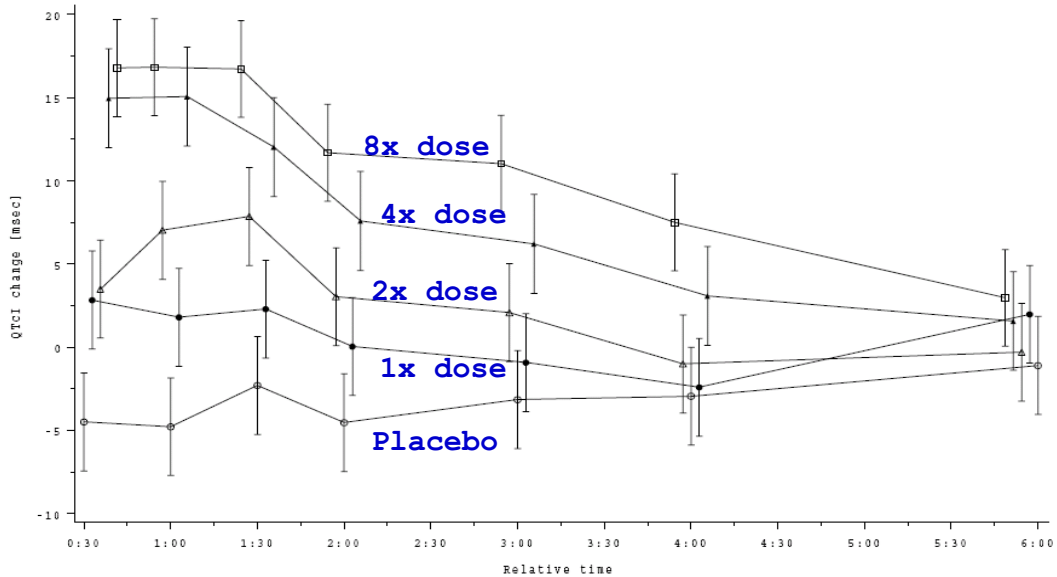
Largest mean effect over time

- Case study **B** for “mild QT prolongation”
- QTcI time-matched change from baseline
- Largest difference: 7.1 ms (with 9.3 ms 95% UCL)



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Dose dependent QTc prolongation Case study C



Results of three drugs

- Mean and Upper Confidence Limit (UCL) of difference to placebo of both methods

Drug		E14 - largest mean change Mean - UCL [ms]	PKQT - change at Cmax Mean - UCL [ms]	<i>Larger</i>
Case Study B	Ther. dose	2.6 - 5.5		
	Sup. dose	7.2 - 9.6		
Case Study C	Dose 1	7.4 - 10.7		
	Dose 2	11.6 - 15.2		
	Dose 4	19.3 - 23.1		
	Dose 8	21.4 - 25.6		

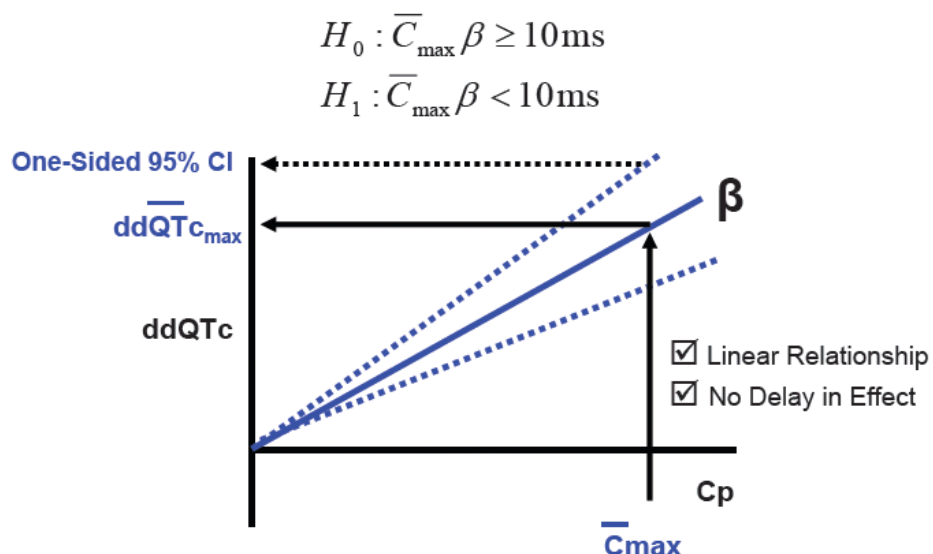
Exposure-Response Modelling

- “Officially” introduced by C. Garnett (FDA) in 2006
 - To investigate the relationship of pharmacokinetic exposure vs. QT(c) change
- 1. Linear approach
 - Use actual concentrations and placebo corrected QTc change from baseline at any point in time
 - Fit a straight line (linear mixed model)
 - Estimate the effect size at the gMean Cmax of therapeutic and suprathreshold dose - and determine 95% UCL

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Exposure-Response Modelling

Derived Metric from C–QTc Relationship



- from Garnett (2006)

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Exposure-Response Modelling

- Main Assumptions of the linear PK-QTc modelling
 - Linear relationship between concentration and QTc effect

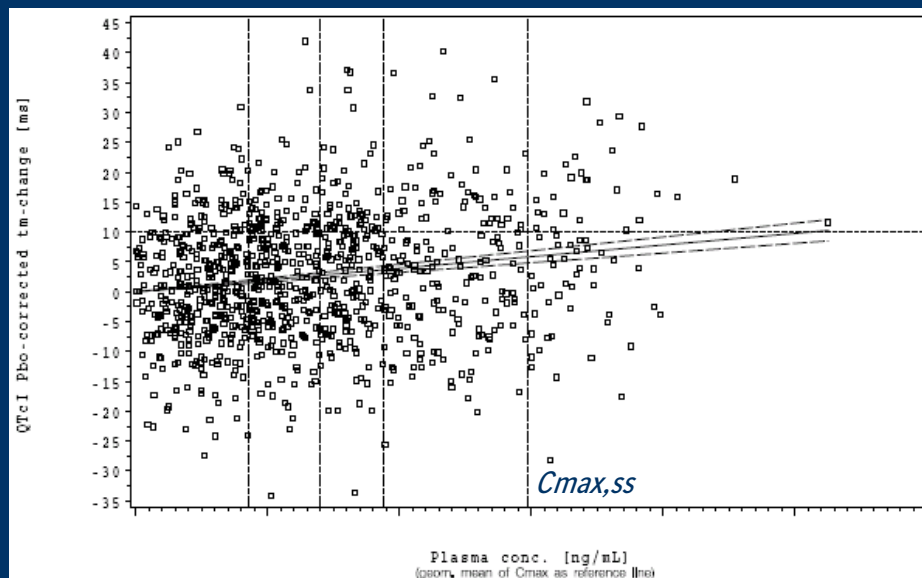
$$QTc\text{-Effect} = E_0 + p * Conc$$

- No delay in effect (Hysteresis)
- No (active) metabolites

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Case study B - reevaluated

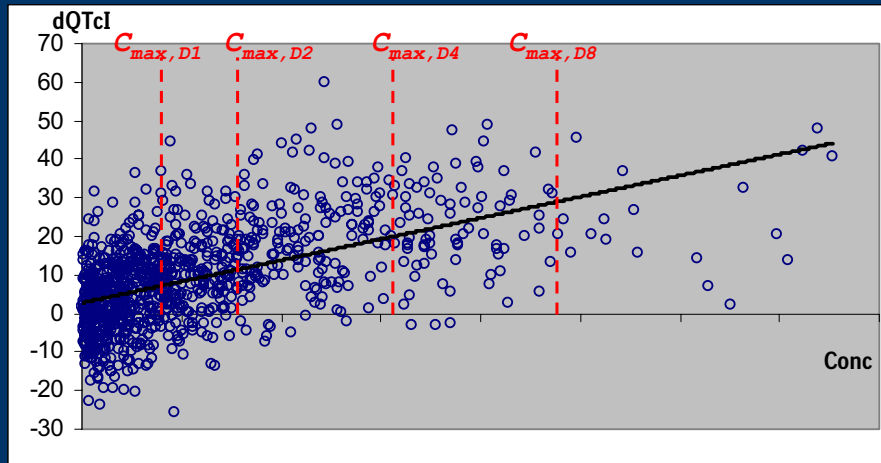
- At C_{max} of supratherapeutic dose: 5.8 ms (95% UCL: 6.9 ms)



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Case study C - reevaluated

- Linear relationship?
- QTcI time matched change from baseline



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Comparison of PKQT and E14

- Mean and Upper Confidence Limit (UCL) of difference to placebo of both methods

Drug		E14 - largest mean change Mean - UCL [ms]	PKQT - change at Cmax Mean - UCL [ms]	Larger
Case Study B	Ther. dose	2.6 - 5.5	3.7 - 4.3	E14
	Sup. dose	7.2 - 9.6	5.7 - 6.6	E14
Case Study C	Dose 1	7.4 - 10.7	5.9 - 6.2	E14
	Dose 2	11.6 - 15.2	9.6 - 10.1	E14
	Dose 4	19.3 - 23.1	19.1 - 20.1	E14
	Dose 8	21.4 - 25.6	30.5 - 31.6	PKQT

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Comparison of PKQT and E14

- Garnett (2008)

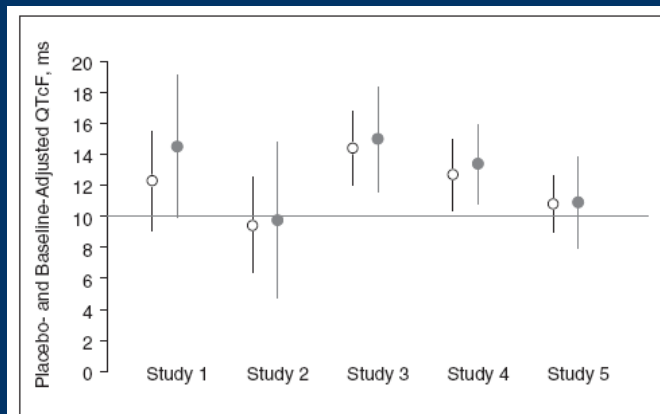
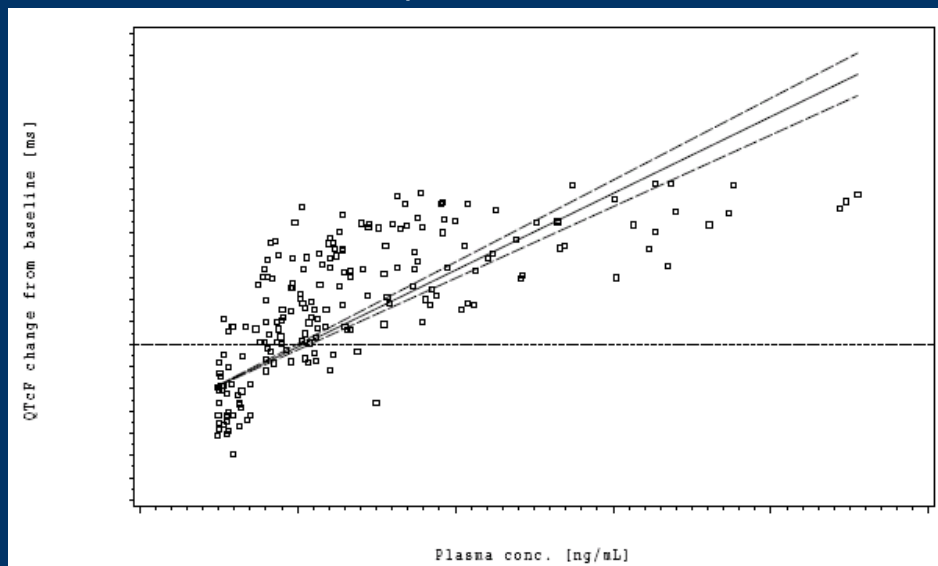


Figure 1. Moxifloxacin mean and 90% confidence intervals of placebo- and baseline-adjusted QTcF computed using the concentration-QT (—○—) and E14 (—●—) methods from 5 thorough QT studies. The solid line at 10 ms indicates the regulatory “no-concern” threshold.

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Case Study D

- Clear non-linear relationship



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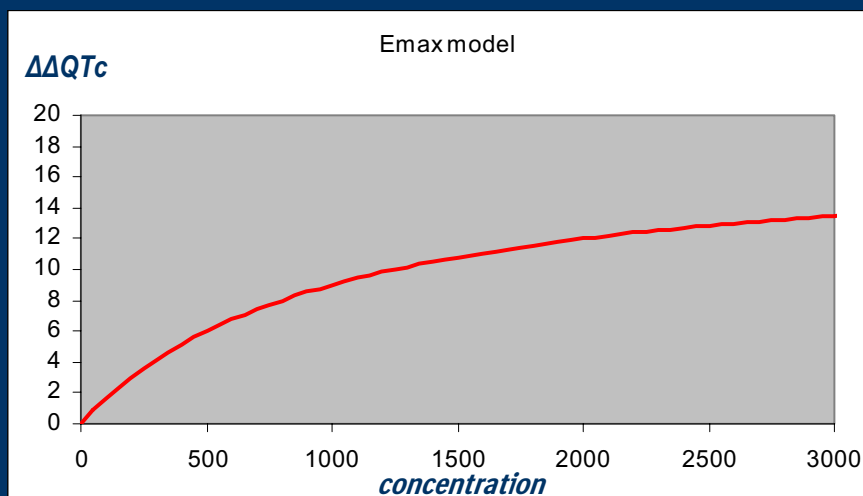
PK-QT modelling: Improvements

- 2. Non-Linear approach
 - Typical effect-relationship: Emax-model
 - Use actual concentrations and placebo corrected QTc change from baseline at any point in time
 - Estimate the effect size at the gMean Cmax of therapeutic and suprathreshold dose - and determine 95% UCL
- Assumption
 - Again: no hysteresis, no active metabolites
- Strong interaction between Statisticians, Pharmacometricians and Clinicians advised

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Emax model, Emax=20 ms, EC50=1000

$$QTc\text{-Effect} = E_0 + (E_{max} * Conc)/(EC_{50} + Conc)$$



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Exposure-Response Modelling

- Emax-modelling for exposure-response relationship
 - Typical model for PKPD

$$QTc\text{-Effect} = E_0 + (E_{max} * Conc)/(EC_{50} + Conc)$$

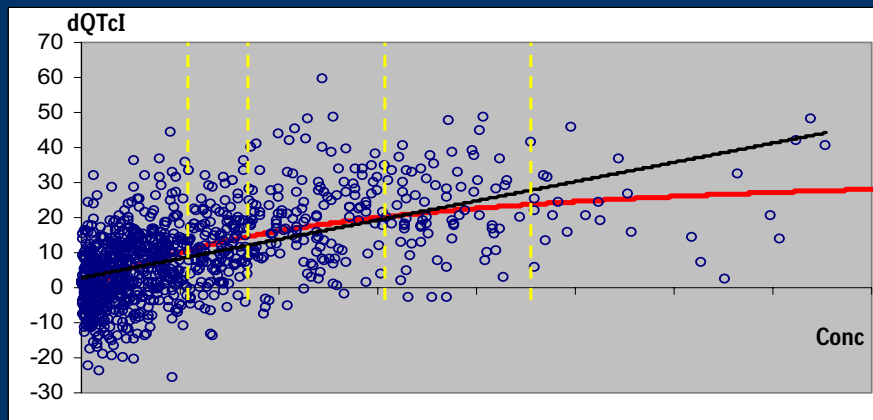
- Conc \approx 0 \rightarrow QTc effect \approx E_0
- Conc \approx EC_{50} \rightarrow QTc effect \approx $(E_0 + E_{max})/2$
- Conc \gg EC_{50} \rightarrow QTc effect \approx $E_0 + E_{max}$

- For low Conc ($\ll EC_{50}$), a linear relationship can be assumed
- For concentrations around EC_{50} , a log-linear relationship is a possible approximation
 - However, the direct application of a nonlinear model is advisable in this case

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Case study C - reevaluated

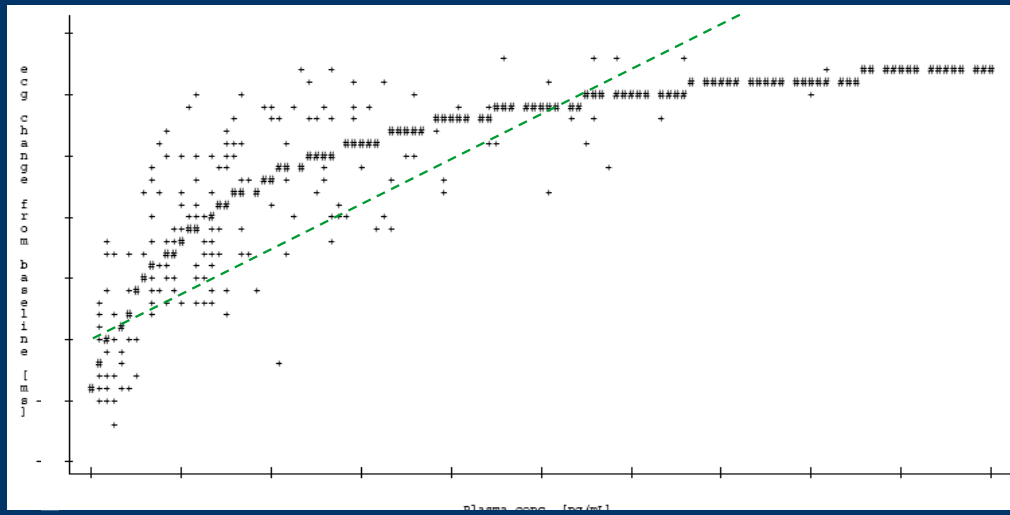
- Non-Linear Emax model is fitting better to the data
- QTc estimates for 3 of the doses almost unchanged
- Emax: 38 ms



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Case study D - reevaluated

- Non-Linear Emax model is clearly better



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PK-QT modelling: Improvements

Emax-type relation is not the only possible PKPD model

- If this model does not fit - try something else (e.g. Hill coefficient)
- Examples for causes of indirect relationship
 - Effect of drug on heart rate
 - Delay due to between blood exposure and target place (distribution)
 - Active metabolites
- Which are relevant, how can they be detected?
- Again: Strong interaction between Statisticians, Clinicians and Pharmacometricians advised

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Stepwise approach in TQT trials

- Perform E14 analysis – largest change from baseline
 - Use repeated measurements analysis for highest statistical efficiency
- If E14 analysis is **clearly** negative – STOP, otherwise explore linear PK-QT model
 - Any indication for a deviation from linearity?
 - If yes, explore non-linear mixed effects model (e.g. Emax)
- Provide hysteresis plots
 - Any indication for delayed effects?
 - If yes, hand-over to NONMEM experts for refined modelling
 - Incorporate analysis NONMEM model (based on existing PK model, if possible)
- **Stepwise allows for putting the capacity, where it is needed**

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Current regulatory position (FDA)

“Regulatory review of QT study is not complete without an assessment of concentration-QTc relationship”

*Norman Stockbridge, M.D., Ph.D.
Director, Cardio-Renal Drug Products
Head, Interdisciplinary Review Team for QT
CDER, FDA*

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Current regulatory position

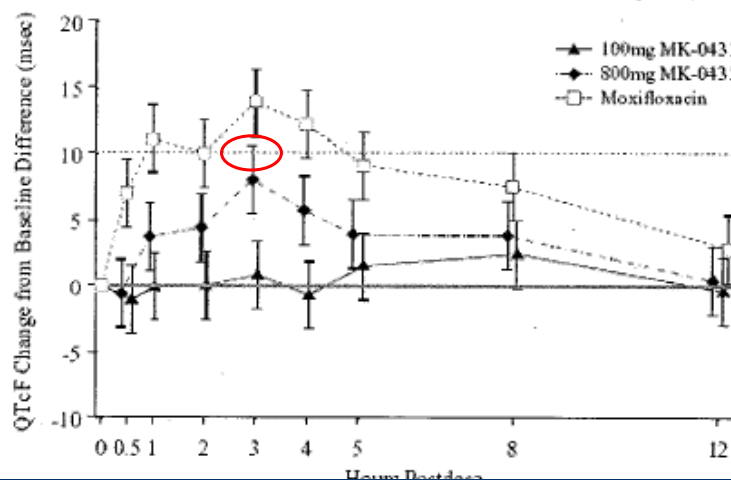
- “If the ‘thorough QT/QTc study’ is **positive**, additional evaluation in subsequent clinical studies should be performed.
- One objective of this evaluation should be to fully describe the effect of the drug on the QT/QTc interval in the target patient population with particular **attention to dose and concentration-related** effects.”

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Specific example: Sitagliptin

- Dose used: 100 mg and 800 mg (8fold therapeutic dose)

Figure 14. Mean (90% CI) QTcF change from baseline differences (active –placebo) for sitagliptin and moxifloxacin treatments and by time point following administration of single oral doses of 100-mg and 800-mg sitagliptin and moxifloxacin to healthy male and female subjects (P032)

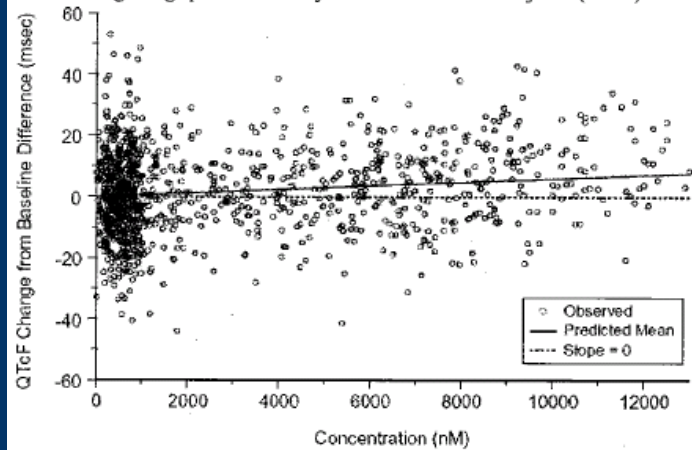


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Specific example: Sitagliptin

- Dose used: 100 mg and 800 mg (8fold therapeutic dose)

Figure 15. Individual QTcF change from baseline (placebo-corrected) values versus plasma sitagliptin concentration and the fitted linear PK/QTc model following administration of single oral doses of 100-mg and 800-mg sitagliptin to healthy male and female subjects (P032)



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Specific example: Sitagliptin

- Dose used: 100 mg and 800 mg (8fold therapeutic dose)
 - Single dose, but worst case (with regard to PK) clearly covered
- E14 result:
 - no QT(c) effect at 100 mg
 - Suprathereapeutic dose:
 - 8ms maximal effect (with 95% UCL of 11 ms) 3 hours post dose
 - / slight prolongation also at the other time points
- Did the sponsor do wrong in selecting a **too high** suprathereapeutic dose?

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Specific example: Sitagliptin

- Did the sponsor do wrong in selecting a **too high suprathapeutic dose**?
- NO: This dose clearly characterized the QT(c) effect of the drug
- PK-QT model came out with an UCL of less than 10 ms
- Label only mentions this characterization of the QTc effect
 - No precaution/warnings with regard to cardiac safety

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Specific example: Sitagliptin

- Other question: If suprathapeutic doses are used to characterise the QT(c) effect, based on a PK-QT model:
Do we still need the therapeutic doses?
- Including therapeutic doses are still recommended: Modelling should be supportive, but not the main analysis (just in case the suprathapeutic dose overshoots the limit)
- Including two doses allows better for checking the inherent assumptions of the models (e.g. linearity)
- Therapeutic pharmacokinetic exposures should not only be a minority of the data material in TQT trials

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Relation to early clinical development

- First Phase I safety studies:
Perform ECG recordings similar to TQT studies
 - Quality controlled ECGs, carefully measured intervals
 - Single ECGs might be sufficient, no positive control
 - Power **not sufficient to show absence** of QTc effect – but when several doses are examined, an indication for presence of QTc effect could be observed with large likelihood

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Relation to early clinical development

- Use these Phase I studies to **establish a PK-QT relationship**
 - Pool data (but be aware of study specific effects)
 - For internal risk evaluation and decision making
 - Also for regulatory review during drug development
 - If no QT liability is likely based on the pooled analysis, the Thorough QT study might be postponed to Phase III
 - Remember the need to ensure the safety of the patients in your studies
- Again: Strong interaction between different functions advised

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Application in oncology

- “There are some drugs that **cannot be studied** in a “thorough QT/QTc study” in healthy volunteers due to safety or tolerability concerns (e.g., cytotoxic cancer drugs). In such cases, the “thorough QT/QTc study” can often be conducted in patient populations.
- When this is not possible, the importance of detecting and modifying this safety risk means that **other ways of detecting effects** on the QT/QTc interval need to be developed. These might include the collection of ECGs at multiple time points under tightly controlled settings that target a **broad range of doses** early in development.”

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Application in oncology

- E14 approach can usually not be applied in oncology
 - Most often, suprathereapeutic doses cannot be studied
- PK-QT modelling could be **the central tool** in this therapeutic area
- Again, collect quality controlled ECGs, carefully measured intervals
 - Phase I patient studies are best options
- Use these studies to establish a PK-QT relationship
 - Characterize the effect potential within the therapeutic window
- Questions on **generalisation** and **extrapolation** of the results **remain**, but less of concern if the drug is effective in the proposed range of pharmacokinetic exposure

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Conclusions

- PK-QT modelling is supportive to E14 analysis in TQT trial
- Analysis assumptions are often fulfilled, but should generally be checked
 - Linearity of effect
 - Delay of effect
- The data rich TQT studies with carefully measured ECG intervals provide a sound basis for developing the PK-QT models (and its methodologies)
 - The situation might be different pre-clinically (be aware of false negative signals from automatic ECG measurements)
- Establishing a PK-QT relationship early on could be supportive for internal decision making and communication with regulators

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Biopharmaceutical forum

- <http://www.biopharmnet.com/cardiac.html>
- Network forum to discuss questions
- Literature on QT evaluation

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Acknowledgements

- Michael Koenen-Bergmann (Clinical)
- Katja Grasmäder, Vincent Duval (Pharmacokinetics)
- Christina Ring (Biostatistics, University of Ulm)
- Patricia Glomb (Biostatistics, University of Heidelberg)

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References

General PKPD

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- Bonate P. Pharmacokinetic-Pharmacodynamic Modeling and Simulation. Springer 2005.

PKQT

- Garnett CE et al. Concentration-QT Relationships Play a Key Role in the Evaluation of Proarrhythmic Risk During Regulatory Review. J Clin Pharmacol., 2008:13-18

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Appendix

BACK-UP

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Current regulatory position (FDA)

Recommendation for submissions to use the Concentration-QTc method:

The approach we recommend is stated briefly as follows: **in most cases, a linear mixed effects modeling approach may be used to quantify the relationship between the plasma concentration (of the parent drug and/or metabolite(s)) and $\Delta\Delta QTc$ (time-matched drug-placebo difference in QTc interval, baseline- adjusted). Based upon this estimated relationship, an estimate of the predicted population average expected $\Delta\Delta QTc$ and its corresponding upper-95% one-sided confidence interval bound at relevant concentration levels may be used to evaluate appropriate concentration levels, e.g. the mean maximum plasma concentrations under therapeutic and supra-therapeutic doses or other concentrations of interest.**

Presentation at 2007 ICSA
Applied Statistics Symposium

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Current regulatory position (FDA)

We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the evaluation of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include the investigation of the validity of ignoring a delayed effect and the justification for the choice of pharmacodynamic model (linear versus non-linear). A description of the statistical properties of the method used to estimate the predicted population $\Delta\Delta QT_c$ values and associated confidence intervals should also be provided. All model codes and data sets to support this analysis should be submitted as SAS transport files (*.xpt) for review.

Presentation at 2007 ICSA
Applied Statistics Symposium

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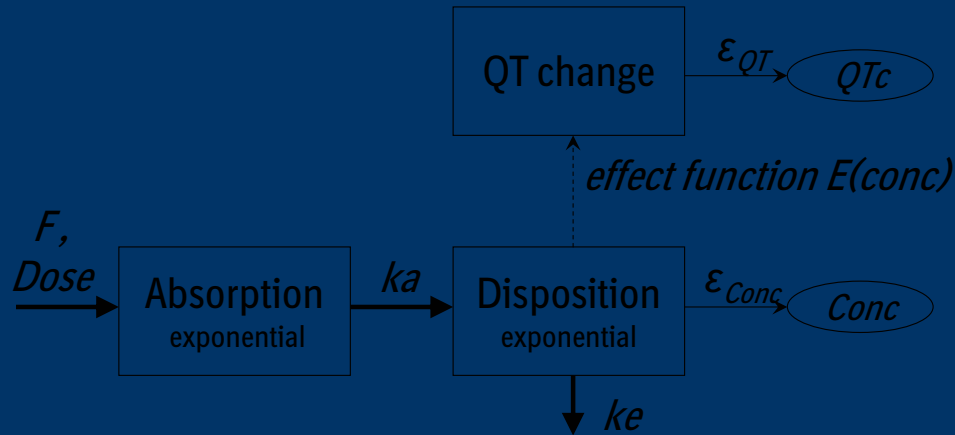
Simulation study

- Simulation study for comparing the outcome of the E14 analysis (Largest change from baseline over time) with the **Linear** PK-QT modelling
- Data simulation of PK and QT data in TQT trial
 - Based on a PK model with a linear concentration-QT effect relationship
 - Sensitivity graphs present the outcome of both approach with respect to changes of the model parameters

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PK model and QT relationship

- PK model: Bateman model with interindividual F , ka and ke
- Linear relationship between concentration and QT change:
 $QT_{change} = E * Conc$; E varies interindividually



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PK model and QT relationship

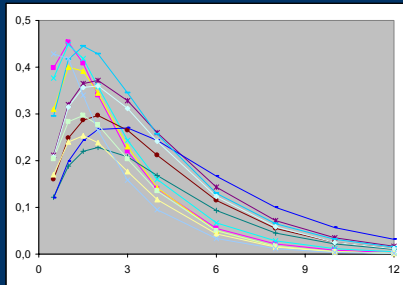
All cases based on a crossover design with placebo and two doses

- PK model:
 - One compartment model after oral administration (Bateman)
 - Interindividual variability of F , ka and ke
 - Relative measurement error for concentration
- PK QT relationship
 - a) Linear relationship between concentration and QT change assumed, based on error-free concentration
 - b) shifted linear relationship to simulate sigmoid shape
 - Interindividual variability of PK-QT-effect
 - Absolute measurement error for QT change from baseline
 - HR assumed to be stable (no effect on QT correction)
- Monte Carlo Simulation with 1,000 replicates for each case

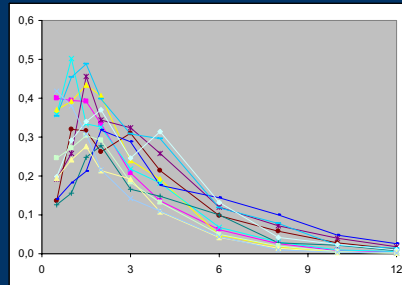
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Example Outcomes of the model (12 subjects)

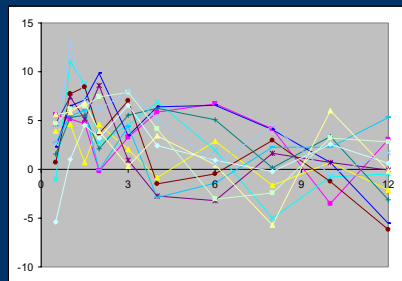
Concentration without error



Concentration with error



delta QTc



Results of simulation studies

- The results of the PK-QT modelling and the E14 analysis are generally similar
- The bias of the PK-QT modelling is smaller than E14, but increases for higher doses
- Performance of PK-QT modelling is better than E14 up to moderate PK measurement error
- PK-QT analysis is sensitive to changes of its assumptions (sigmoid effect) and may underestimate the QTc effect, while E14 is very robust to those changes