

Spring 2008 series

Introduction

- Alex Dmitrienko (Eli Lilly and Company), Chair of Distance Training, Biopharmaceutical Section of ASA

Assessment of QTc prolongation in clinical drug development

- Alex Dmitrienko (Eli Lilly and Company)
- Thursday, May 22 (noon-2:00 Eastern time)

Handouts

- Can be downloaded from BioPharmNet's web site at <http://www.biopharmnet.com/doc/doc03002-03.html>

Alex Dmitrienko

Research Advisor

- Global Statistical Sciences, Eli Lilly and Company

Cardiac safety/QTc prolongation issues

- Since 1998

PhRMA QT Statistical Expert Team

Publications

- Analysis of QTc interval in clinical trials

Assessment of QTc prolongation in clinical drug development

Alex Dmitrienko

Biopharmaceutical Section's web-based training program

May 22, 2008

Webinar's web page

Web page set up for this webinar

<http://biopharmnet.com/doc/doc03002-04.html>

Supplementary material

Handouts

References

Links

SAS code

White paper

Design and Analysis of Thorough QT Studies

by Alex Dmitrienko, Charles Beasley and Malcolm Mitchell

Facilitate an open discussion of statistical and non-statistical issues related to the design and analysis of thorough QT studies

Download a free copy

<http://biopharmnet.com/doc/doc14003.html>

3

Cardiac safety knowledge hub

Biopharmaceutical Network

Collaboration, novel scientific solutions and knowledge sharing

Cardiac Safety knowledge hub

<http://biopharmnet.com/cardiac.html>

Annotated bibliography

Key publications that deal with cardiac safety issues

<http://biopharmnet.com/doc/doc14001.html>

4

Interactive format

My objective

Discuss assessment of QTc prolongation in clinical trials

Your objective

Share your thoughts/information

Feedback

Send an e-mail to ecg@biopharmnet.com

5

Outline

A

Background information

B

Design considerations

C

Analysis considerations

6

Design considerations

	Regular study	Thorough QT study
Control of QTc variability	✓	✓
Study design		✓
Definition of QTc treatment difference	✓	✓
Sample size calculations		✓
ECG acquisition schedule	✓	✓

7

Analysis considerations

	Regular study	Thorough QT study
Peak QTc effect and reverse multiplicity		✓
Classification of QTc effects		✓
QT correction	✓	✓
QTc-exposure analysis	✓	✓

8

What will not be discussed

Manual versus machine measurements

Machine measurements may be less accurate but tend to be more reproducible

Standard ECGs versus continuous ECGs

Focus on standard 12-lead ECGs

Positive control and assay sensitivity analysis (thorough QT studies)

Important issues that need to be discussed elsewhere

9

Module A

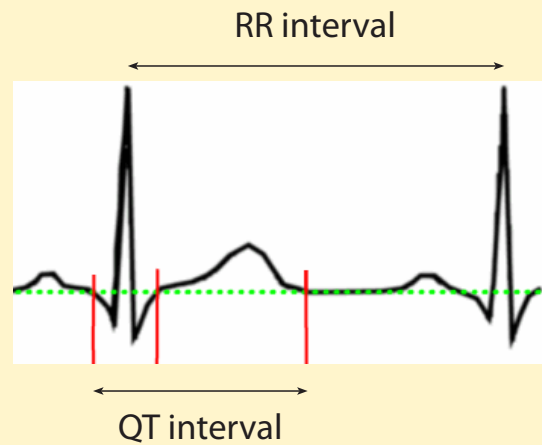
A

Background information

10

Module A

QT interval is measured on a 12-lead ECG



Two complexes from a standard electrocardiogram (ECG)

11

Module A

QTc interval is corrected for heart rate

Factors influencing length of QT interval

Heart rate (most pronounced), demographic characteristics (gender and BMI), conditions

Heart rate correction

QTc interval = QT interval corrected for heart rate (RR interval)

Details

Discussed in Module C [QT correction]

12

Module A

QTc interval is a biomarker of TdP

Torsades de Pointes
(ventricular tachycardia)

Villain
(outcome of interest)

QTc interval

Sidekick
(marker)

13

Module A

Relationship between QTc and TdP

What I think has been established is that the QTc interval duration itself is not a sufficient condition to cause TdP

The imprecise value of the QT interval as a predictor of clinical events seems brutally clear

Lipicky (2005)

14

Module A

Why is QTc interval still used?

QTc interval is not perfect

Viewed as the best available marker for TdP

Assessment of pro-arrhythmic risks in clinical trials is based on QTc interval

Most common cause for drug withdrawal

Prolongation of QTc interval is the most common cause for drug withdrawal

Further reading

Lipicky (2005)

Assessment of QTc interval in regular and thorough QT studies

Regular studies

Until recently, QTc interval was viewed as a standard safety parameter

Thorough QT studies

First introduced in 2002 and included in ICH E14 (based on a terfenadine QT study conducted in 1991)

Main tool for the evaluation of QTc liability

Thorough QT studies

Are thorough QT studies required for all compounds?

Generally required for all new compounds with systemic bioavailability

Known exceptions

Antiarrhythmic drugs

Monoclonal antibodies

Other potential exceptions

17

Module A

QTc assessment standards in clinical trials

Changes in QTc assessment standards

Data mining exercise to potentially relax clinical trial requirements for performing QT interval assessments (Food and Drug Law Institute annual meeting, March 27, 2008)

Proposals and suggestions

Optimize the design and analysis of thorough QT studies

Optimize clinical QTc evaluation in general

18

Module A

Module B

B

Design considerations

19

Module B

Outline

	Regular study	Thorough QT study
Control of QTc variability	✓	✓
Study design		✓
Definition of QTc treatment difference	✓	✓
Sample size calculations		✓
ECG acquisition schedule	✓	✓

20

Module B

Control of QTc variability

Reduce background QTc variability

Due to large variety of influences (circadian trends, food effect, population-specific variability, etc)

Remove these sources of QT variability

Reduce QTc measurement variability

Due to difficulties in precision of measurement

Signal averaging

Circadian variability

Spontaneous variability

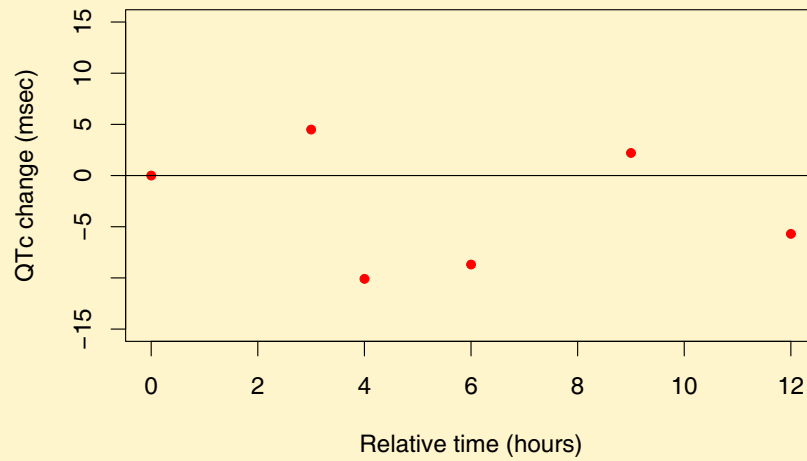
Normal physiological variability during the course of a day

Magnitude

Range of within-subject QTc changes up to 60 msec (Morganroth, 1991)

In clinical practice spontaneous within-subject QTc changes are typically smaller in magnitude

Circadian variability



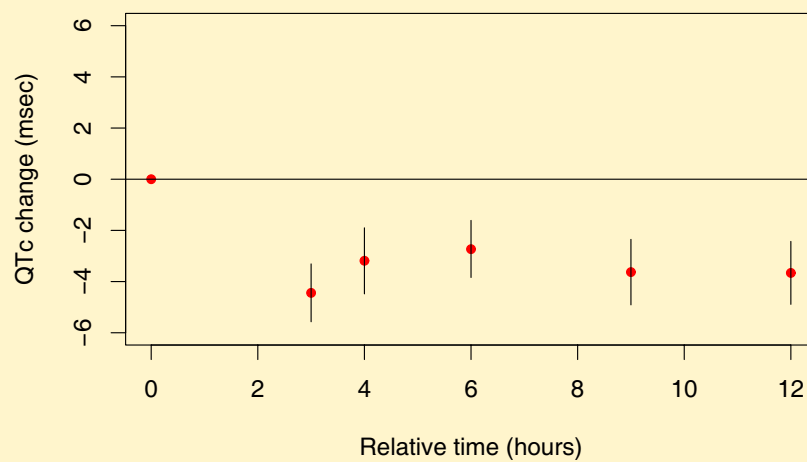
Within-subject QTc changes relative to 0-hour time point
(single subject, 6 post-dose time points)

23

Module B

Control of QTc variability

Circadian trends



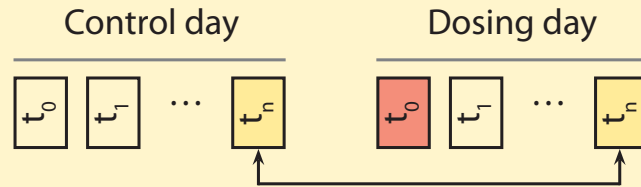
Mean QTc changes relative to 0-hour time point
(95% CIs, 90 subjects)

24

Module B

Control of QTc variability

Time-matched ECG recordings



QTc measurements on the dosing day are compared in a time-matched manner to QTc measurements on the control day

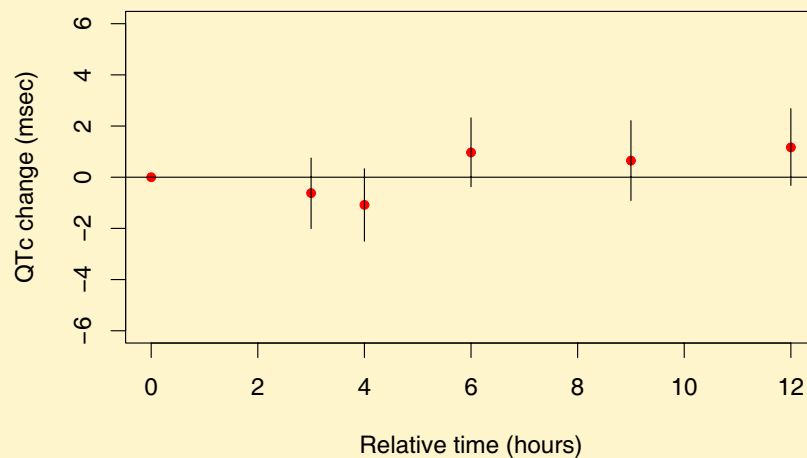
■ Test drug is administered at t_0

25

Module B

Control of QTc variability

Time-matched analysis



Time-matched mean QTc changes relative to 0-hour time point (95% CIs, 90 subjects)

26

Module B

Control of QTc variability

Controlled environment

Other sources of QT variability

Eating, drinking, sleeping, exercise must be controlled

Food effect

Consumption of a meal lengthens QTc interval (Nagy et al, 1997)

Overnight fast prior to receiving the test drug

Fast until the lunch meal or pharmacokinetic t_{\max}

27

Module B

Control of QTc variability

Signal averaging

Strengthen QTc signal

Average QTc values collected every approximately every minute around each point of ECG acquisition

Examples

3 replicates (tolterodine QT study, Malhotra et al, 2007)

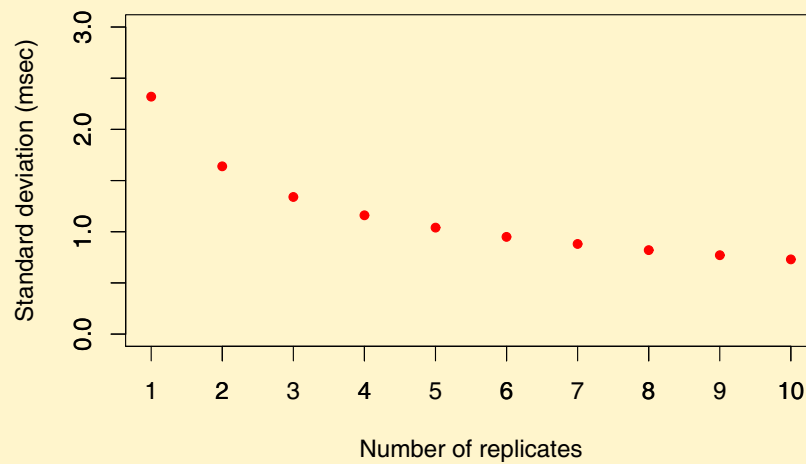
10 replicates (tadalafil QT study, Beasley et al, 2005)

28

Module B

Control of QTc variability

Measurement error and number of replicates



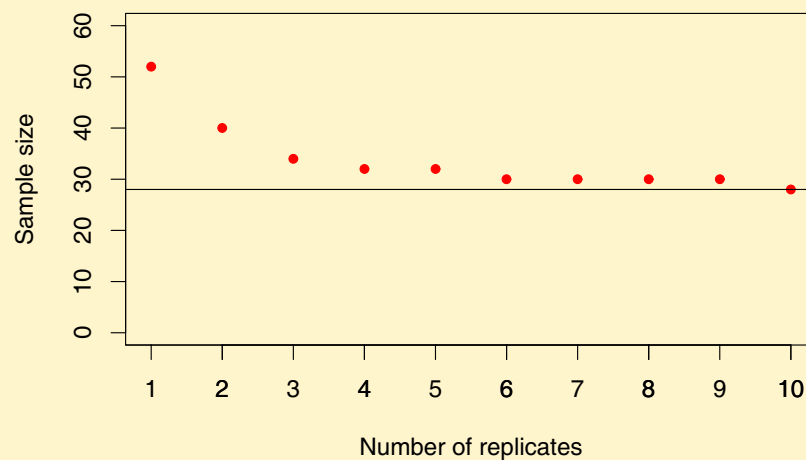
Standard deviation of measurement variability as a function of the number of replicates

29

Module B

Control of QTC variability

Sample size and number of replicates



Total sample size in a cross-over study using a single-delta definition of treatment difference (Definition S, 95% power, 5 msec treatment difference)

30

Module B

Control of QTC variability

Number of replicates

Recommendation

3-5 replicates are generally recommended

Account for key study features

Subject population

Definition of the treatment difference

Determine variance components and select a population- and design-specific number of replicates

Further reading

Zhang, Dmitrienko and Luta (2008)

Study design

Study design objectives

Single-dose and multiple-dose designs

Number of doses (therapeutic and suprathreshold dose levels)

Selection of a study design

Parallel versus cross-over designs

Types of cross-over designs

Balanced designs versus unbalanced designs

Williams design in thorough QT studies

Study design objectives

Multiple objectives

Adequate plasma concentrations (single-dose design versus multiple-dose design aimed at achieving a steady state level)

Determination of a tolerable dose (dose-titration design aimed at determining a subject-specific maximum tolerated dose)

33

Module B

Study design

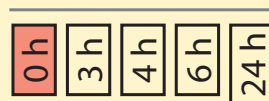
Single-dose design


Example

Tadalafil QT study (Beasley et al, 2005)

Well-tolerated test drug with no active metabolites

Day 1



 Test drug is administered at 0 h

34

Module B

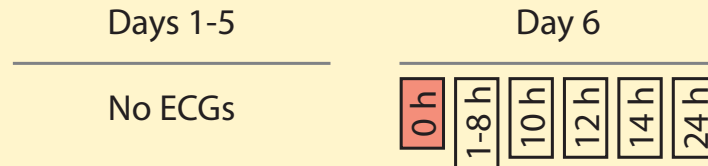
Study design

Multiple-dose design (steady-state assessment)

Example

Darifenacin QT study (Serra et al, 2005)

Longer half-life or one or more metabolites



Test drug is administered at 0 h
(half-life is 13-19 hours and
steady-state levels are reached within 6 days)

35

Module B

Study design

Multiple-dose design (tolerability assessment)

Example

Duloxetine QT study (Zhang et al, 2007)

Unknown tolerability at higher doses

60 mg, 120 mg

160 mg, 200 mg

Days 1-4

Days 1-3

Day 4

No ECGs

No ECGs



Test drug is administered at 0 h and 12 h
(steady-state levels are reached within 3 days)

36

Module B

Study design

Number of dose levels

Supratherapeutic dose level

Achieve the highest exposure levels anticipated in clinical practice

Link between healthy subjects and patients with the disease

Substantial multiple

5-fold increase over the therapeutic dose (e.g., tadalafil QT study)

Exceptions: Tolerability issues at higher doses (tolterodine QT study)

37

Module B

Study design

Number of dose levels

Therapeutic dose is commonly used in thorough QT studies

Better understand the dose-response relationship or QTc-exposure relationship (vardenafil QT study, Morganroth et al, 2004)

Fallback strategy if QTc prolongation at supratherapeutic dose

Therapeutic dose is not required

Not needed if no QTc prolongation effect is expected

38

Module B

Study design

Parallel and cross-over designs

Cross-over designs

Washout period is not excessively long

Length of each treatment period is short

Parallel designs

Longer half-lives or treatment periods

Relatively uncommon in thorough QT studies
(darifenacin QT study)

Types of cross-over designs

Balanced cross-over designs

Balance for carry-over effects is required

Each treatment precedes every other treatment, excluding itself, equally often

Example

Balanced Williams design (Williams, 1949)

One-square design (therapeutic dose, suprathreshold dose, positive control and placebo)

Two-square design (suprathreshold dose, positive control and placebo)

One-square Williams design

Sequence	Treatment assignment
1	PTSC
2	TCPS
3	SPCT
4	CSTP

Therapeutic dose (T), suprathreshold dose (S),
positive control (C), placebo (P)

41

Module B

Study design

Two-square Williams design

Sequence	Treatment assignment
1	PSC
2	SCP
3	CPS
4	CSP
5	PCS
6	SPC

Suprathreshold dose (S), positive control (C), placebo (P)

42

Module B

Study design

Definition of QTc treatment difference

Treatment difference

Impacts study design, including sample size

Selection criteria

Minimize the standard error of treatment effect estimates (width of confidence intervals)

Minimize the bias of treatment effect estimates

Classification of treatment difference definitions

Time-matched definitions

Single-delta definitions

Double-delta definitions

Triple-delta definitions

Other definitions

Not based on time-matched analysis (Glomb and Ring, 2008)

Clinical trial example

Cross-over design

Three-period design (supratherapeutic dose, positive control and placebo)

Each period includes a lead-in day and a single dosing day

Treatment comparison

Test drug versus placebo

45

Module B

Definition of QTc treatment difference

Clinical trial example

Test drug period

Day A

Day B




Placebo period

Day C

Day D



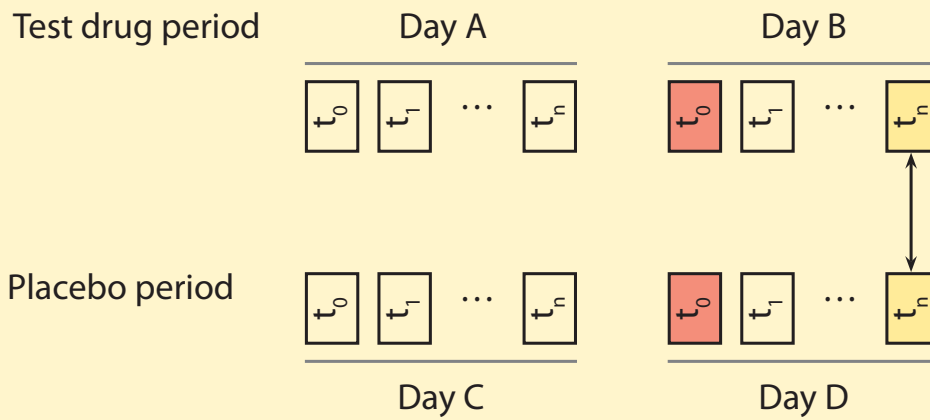
 Test drug/placebo are administered at t_0

46

Module B

Definition of QTc treatment difference

Single-delta definition (Definition S)



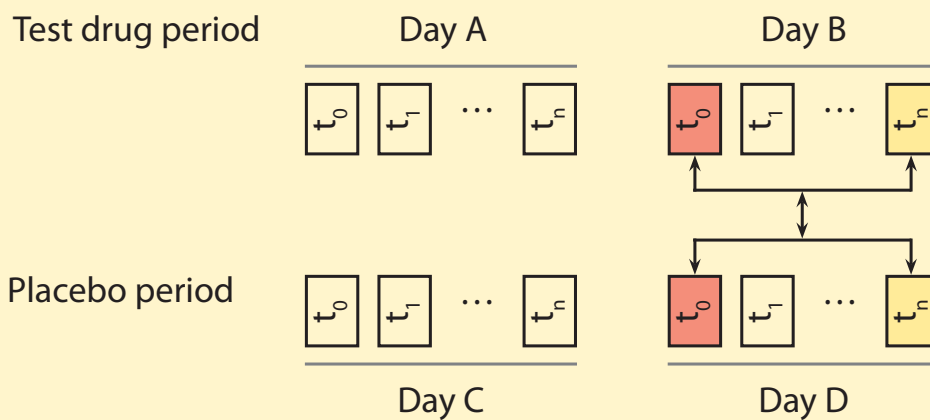
$$\text{Treatment difference} = B_n - D_n$$

47

Module B

Definition of QTc treatment difference

Double-delta definition (Definition D1)



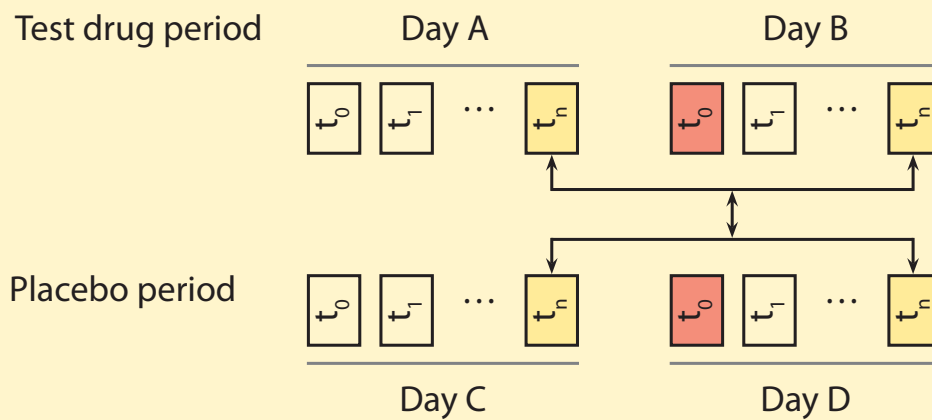
$$\text{Treatment difference} = (B_n - B_0) - (D_n - D_0)$$

48

Module B

Definition of QTc treatment difference

Double-delta definition (Definition D2)



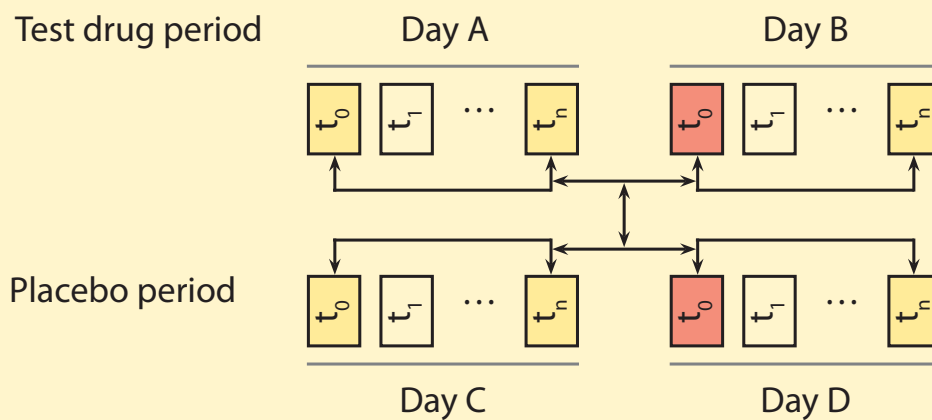
$$\text{Treatment difference} = (B_n - A_n) - (D_n - C_n)$$

49

Module B

Definition of QTc treatment difference

Triple-delta definition (Definition T)



$$\text{Treatment difference} = [(B_n - B_0) - (A_n - A_0)] - [(D_n - D_0) - (C_n - C_0)]$$

(aka placebo-subtracted time-matched change from baseline)

50

Module B

Definition of QTc treatment difference

Adjustments for covariates

Single-delta definition

Covariates can be introduced in the definition of a treatment difference, e.g.,

B_0 and D_0

A_n and C_n

Double- and triple-delta definitions

Covariate-adjusted definitions can be constructed in a similar manner

Sample size calculations

Flexible framework that accounts for

Study design (parallel and cross-over designs)

Number of ECG replicates

Number of post-dose ECG recordings

Subject population (males, females and mixed)

Further reading

Zhang, Dmitrienko and Luta (2008)

Four thorough QT studies

Three-period design

Suprathreshold dose, positive control and placebo

Study design objectives

Single-dose designs (Studies 1, 3, 4) and dose-titration design (Study 2)

Number of lead-in days

2 lead-in days (Study 1), 1 lead-in day (Studies 3, 4)

Replicate ECGs

10 replicates (Study 1), 4 replicates (Studies 2, 3, 4)

53

Module B

Sample size calculations

Demographic characteristics

	Gender		Age
	Males	Females	
Study 1	99	—	18-53
Study 2	—	117	19-74
Study 3	46	40	18-70
Study 4	30	30	18-63

34,913 drug-free ECG recordings (lead-in days, placebo period) were used in the analysis

54

Module B

Sample size calculations

Estimation of variance components: Assumptions

QT correction method

Fridericia correction (will be discussed in Module C [QT correction])

Multivariate normal distribution

Serial measurements within a day are assumed to be equicorrelated (compound symmetry covariance structure)

55

Module B

Sample size calculations

Estimation of variance components: Model

Fixed effects

Day

Time

Random effects

Subject

Interaction terms (subject-by-day, subject-by-time and subject-by-day-by-time)

Error term

56

Module B

Sample size calculations

Variance component estimates by study

	Study				All studies
	1	2	3	4	
Subject	9.7	13.8	13.7	11.0	12.3
Subject-by-day	3.6	5.3	4.2	4.1	4.2
Subject-by-time	2.1	1.9	2.5	1.7	2.1
Subject-by-day-by-time	3.0	4.1	2.6	2.5	3.1
Error	5.5	5.5	5.0	5.3	5.4

Standard deviations of variance components (msec)

57

Module B

Sample size calculations

Variance component estimates by gender

	Gender	
	Males	Females
Subject	11.4	13.0
Subject-by-day	3.6	5.1
Subject-by-time	2.1	1.9
Subject-by-day-by-time	2.9	3.9
Error	5.5	5.4

Standard deviations of variance components (msec)

58

Module B

Sample size calculations

Sample size calculations for cross-over studies

Key factors

Subject population

Definition of QTc treatment difference (single-, double- and triple-delta definitions)

Number of ECG replicates

Number of post-dose time points

Focus on a basic case (single post-dose time point)

Extensions to multiple post-dose time points
(Zhang, Dmitrienko and Luta, 2008)

59

Module B

Sample size calculations

Sample size formula

Noninferiority objective

Upper limit of a one-sided 95% confidence interval for the mean QTc effect is less than 10 msec (will be discussed in Module C [Peak QTc effect])

Total number of subjects

$$n = (z_{0.95} + z_{1-\beta})^2 \sigma^2 / (c - \Delta)^2$$

c, noninferiority margin, c = 10

1-β, power

Δ, true mean difference

σ², variance of treatment difference

60

Module B

Sample size calculations

Treatment difference definitions

Definition	Variance
S	$2(\sigma_E^2 / r + \sigma_{SD}^2 + \sigma_{SDT}^2)$
D1	$4(\sigma_E^2 / r + \sigma_{SDT}^2)$
D2	$4(\sigma_E^2 / r + \sigma_{SD}^2 + \sigma_{SDT}^2)$
T	$8(\sigma_E^2 / r + \sigma_{SDT}^2)$

Standard deviations: Subject-by-day (σ_{SD}),
 Subject-by-day-by-time (σ_{SDT}), Error (σ_E)
 Number of replicates, r

61

Module B

Sample size calculations

Total sample size by subject population

Population	Treatment difference definition			
	S	D1	D2	T
Males	30	34	58	66
Females	46	46	90	88
Mixed	34	36	66	70

95% power ($\beta = 0.05$), true mean difference $\Delta = 5$ msec,
 3 replicates

62

Module B

Sample size calculations

Total sample size by number of replicates

Number of replicates	Treatment difference definition			
	S	D1	D2	T
1	52	70	102	138
3	34	36	66	70
5	32	30	60	56
7	30	26	58	50
9	30	26	56	48

95% power ($\beta = 0.05$), true mean difference $\Delta = 5$ msec,
mixed population

"Optimal" choice of the number of replicates

Definition D1

$$\text{Variance} = 4(\sigma_E^2 / r + \sigma_{SDT}^2)$$

"Optimal" value of r is determined by σ_E / σ_{SDT}

Ratio is smaller

r has less impact on the power

Example: $(\sigma_E / \sigma_{SDT})^2 = 1.4$ in female-only studies

Ratio is larger

Larger value of r to improve the power

Example: $(\sigma_E / \sigma_{SDT})^2 = 1.9$ in male-only studies

Sample size calculations

Basic case

Focused on a basic case (single post-dose time point)

General conclusions

Subject population: Larger sample size in female-only studies

Definition of QTc treatment difference: Definitions S and D1 are more attractive

Number of ECG replicates: "Optimal" number is population- and design-specific

ECG acquisition schedule

Number and timing of ECG recordings

Driven by pharmacokinetic and pharmacodynamic properties of the test drug

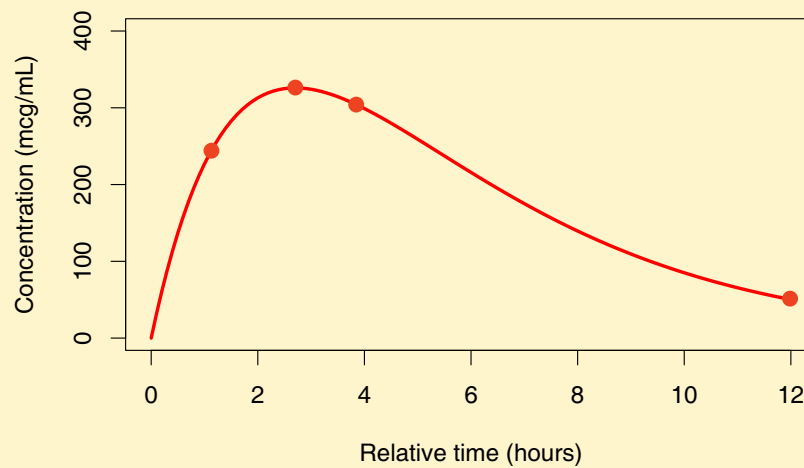
In an ideal world

Based on the time course of drug-related QTc changes (e.g., before, around and after pharmacodynamic t_{\max})

In practice

Based on pharmacokinetic parameters (e.g., before, around and after pharmacokinetic t_{\max})

ECG acquisition schedule: Example



Time course of plasma concentration changes and
ECG acquisition schedule

67

Module B

ECG acquisition schedule

Number of ECG recordings

More frequent ECG recordings

Pharmacokinetic t_{\max} is variable

Delayed QTc effect (will be discussed in Module C
[QTc-exposure analysis])

Active metabolites

Example

Levetiracetam QT study (Hulhoven et al, 2008)

ECG acquisition schedule: 0.5, 1, 1.5, 2, 4, 6, 12 and
24 hours post-dose

Pharmacokinetic t_{\max} is 1.5 hours

68

Module B

ECG acquisition schedule

Number of ECG recordings

Time course of QTc changes

To better characterize the time course of QTc changes, more ECG recordings are needed

Power loss

Due to reverse multiplicity, increasing the number of ECG recordings leads to power loss (reverse multiplicity is discussed in Module C [Peak QTc effect and reverse multiplicity])

69

Module B

ECG acquisition schedule

Module C

C

Analysis considerations

70

Module C

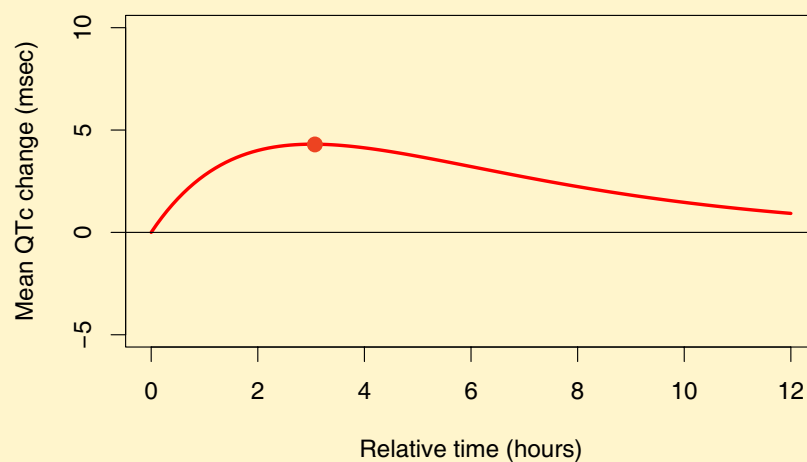
Outline

	Regular study	Thorough QT study
Peak QTc effect and reverse multiplicity		✓
Classification of QTc effects		✓
QT correction	✓	✓
QTc-exposure analysis	✓	✓

71

Module C

Estimation of QTc effect: State trooper principle



Mean time-matched QTc effect
(test drug vs placebo)

72

Module C

Peak QTc effect and reverse multiplicity

Definition of a negative thorough QT study

A negative 'thorough QT/QTc 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 10 ms

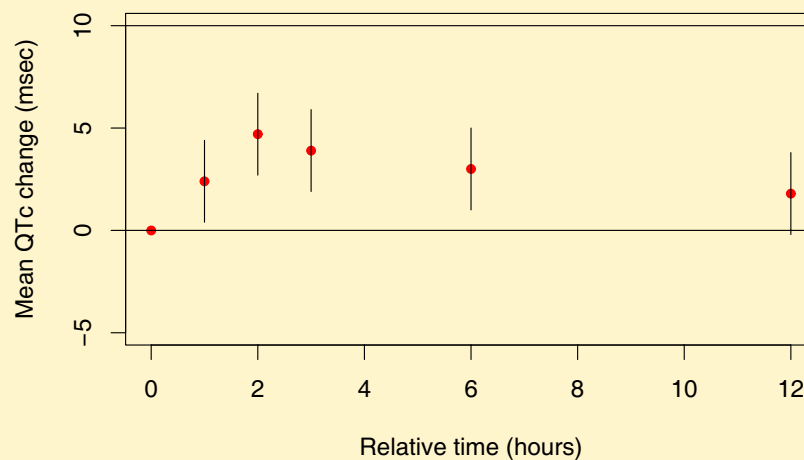
ICH E14 (Section 2.2.4)

73

Module C

Peak QTc effect and reverse multiplicity

Popular interpretation



Upper limits are less than 10 msec

74

Module C

Peak QTc effect and reverse multiplicity

Popular interpretation: Properties

Biased estimate

Estimate of peak QTc effect is biased upward

Error rate

Probability of incorrectly concluding that the QTc effect is present is inflated

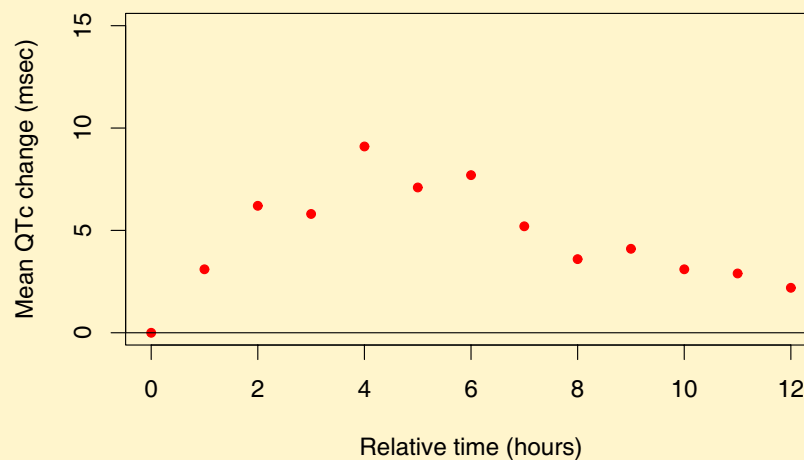
Reverse multiplicity (Offen et al, 2007)

75

Module C

Peak QTc effect and reverse multiplicity

Simulation study



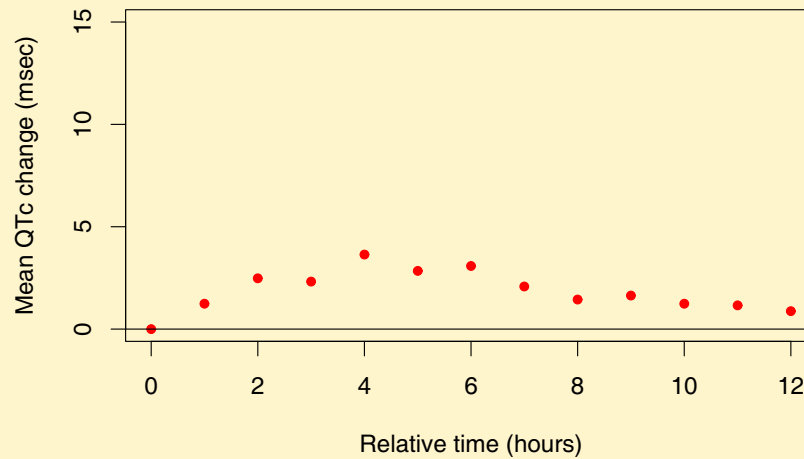
Mean time-matched QTc differences
(moxifloxacin 400 mg vs placebo)

76

Module C

Peak QTc effect and reverse multiplicity

Simulation study



Null hypothesis: Smaller treatment effect,
same correlation structure

77

Module C

Peak QTc effect and reverse multiplicity

Simulation results: Error rate

Time points	Error rate (%)
1 time point (4 h)	3.4
3 time points (every hour from 3–5 h)	5.6
5 time points (every hour from 2–6 h)	8.3
7 time points (every hour from 1–7 h)	9.2
9 time points (every hour from 1–9 h)	9.5

Error rate doubles with 5 or more time points
(compared to a single time point)

78

Module C

Peak QTc effect and reverse multiplicity

Number of post-dose time points

More post-dose time points

Higher error rate

Time-course of QTc changes is better characterized

Example: 12 time points (alfuzosin QT study, Extramiana et al, 2005)

Fewer post-dose time points

Lower error rate

Can still identify peak QTc effect if reliable historical data are available

Example: 5 time points (vardenafil QT study)

79

Module C

Peak QTc effect and reverse multiplicity

Alternative interpretation

Problem with popular interpretation

Multiplicity is working against us

How to account for multiplicity?

Multiplicity-adjusted confidence interval for peak QTc effects

Recent publications (Eaton et al, 2006; Boos et al, 2007; Cheng et al, 2008)

80

Module C

Peak QTc effect and reverse multiplicity

Alternative interpretation: Example

Thorough QT study example (Boos et al, 2007)

4-period cross-over design

9 post-dose time points

Point estimate

Largest mean time-matched difference, 5.5 msec

Upper confidence limit

Naïve limit, 11.0 msec

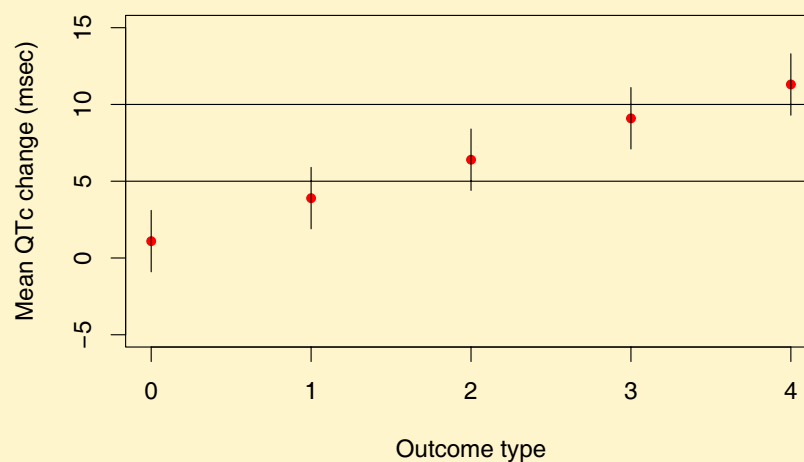
Multiplicity-adjusted limits, 9.2–9.4 msec

81

Module C

Peak QTc effect and reverse multiplicity

Classification of outcomes



Hierarchy of desired outcomes in thorough QT studies

82

Module C

Classification of outcomes

Classification of outcomes

Type 0, 1 and 2 outcomes

Consistent with ICH E14 definition of a negative study

Depending on patient population/condition, Type 2 outcome may result in adverse labeling

Type 3 and 4 outcomes

Test drug affects ventricular repolarization

Unacceptable for benign conditions

May be acceptable for drugs that provide substantial benefit over existing therapies

Classification of outcomes

Example

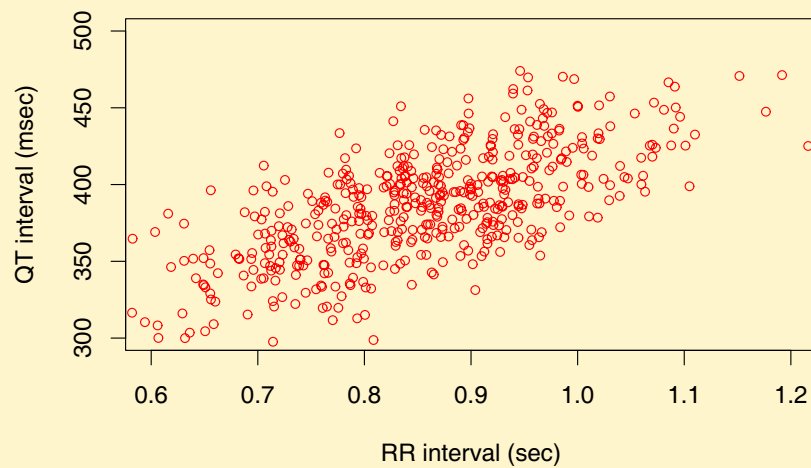
Dmitrienko, Beasley and Mitchell (2008, Sec 2.3)

Comparison of product labels

Tadalafil QT study: Type 0 outcome (mean difference, 2.8 msec; upper confidence limit, 4.4 msec)

Vardenafil QT study: Type 2 outcome (mean difference, 6 msec; upper confidence limit at the suprathreshold dose, 8 msec)

QT correction for heart rate



QT interval shortens when RR interval shortens
(RR interval is the inverse of heart rate)

85

Module C

QT correction

QT correction methods

Heart rate correction

QT_c is QT value corresponding to heart rate of 60 bpm (RR interval of 1 sec)

Correction methods

Fixed/traditional methods

Population/study-specific methods

Individual/subject-specific methods

Model-based methods

86

Module C

QT correction

Fixed QT correction methods

Log-linear corrections

Bazett correction (Bazett, 1920)

$$QT_c = QT / RR^{1/2}$$

Fridericia correction (Fridericia, 1920)

$$QT_c = QT / RR^{1/3}$$

Linear corrections

Framingham correction (Sagie et al, 1992)

$$QT_c = QT + 0.154 (1 - RR)$$

87

Module C

QT correction

Performance of fixed QT corrections

Biased estimates of QT_c effect

Assumed QT-RR relationship is different from true QT-RR relationship

Test drug induces heart rate changes

Alfuzosin QT study

Mean heart rate increase, 3.7 bpm

Upper confidence limit for mean QT_c change:

Bazett correction, 14.4 msec

Data-based corrections, 2.5–4.7 msec

88

Module C

QT correction

Performance of fixed QT corrections

Tolterodine QT study

Mean heart rate increase, 6.3 bpm

Upper confidence limit for mean QTc change:

Bazett correction, 15.8 msec

Fridericia correction, 9.8 msec

Data-based correction, 12.2 msec

Population/study-specific QT correction methods

Data

Based on all off-treatment ECG recordings

Linear correction

Model: $QT = a + b RR + \text{error}$

Correction: $QTc = QT + b (1 - RR)$

Random subject terms is included if multiple ECGs per subject

Log-linear correction

Model: $\log QT = a + b \log RR + \text{error}$

Correction: $QTc = QT / RR^b$

Individual/subject-specific QT correction methods

Data

Based on each subject's off-treatment ECG recordings

Linear and log-linear corrections

Based on formulas similar to population corrections

Regulatory perspective

Recommended in ICH E14 (Section 3.1.2)

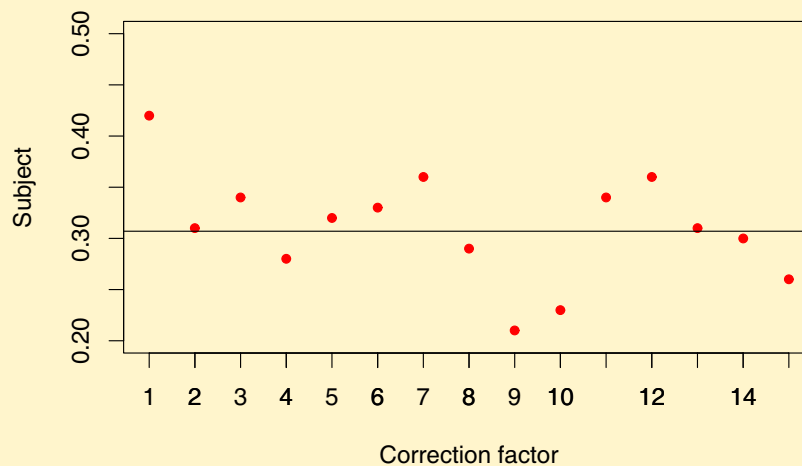
Used in majority of thorough QT studies

91

Module C

QT correction

Comparison of population and individual QT corrections



Correction factor f in population and individual log-linear corrections

92

Module C

QT correction

Individual QT corrections: Number of ECG recordings

General recommendation

20-30 ECGs recordings per subject

Example: 6 ECGs recordings x 4 days

Unreliable with less than 10 ECGs per subject

Key factors

Wide range of RR/heart rate values

Low QT variability

93

Module C

QT correction

Model-based QT correction methods

Data

Based on all ECG recordings (off-treatment and on-treatment)

Linear corrections

Model: $\Delta QT = \text{treatment} + b \Delta RR + \text{error}$

QT correction is not explicitly computed

Estimate of treatment difference

Advantages

Accounts for repeated measures

Accounts for drug-induced heart-rate changes

94

Module C

QT correction

Model-based QT corrections

Assumption

Test drug does not affect the slope of QT-RR relationship (b is constant)

How restrictive is this assumption?

All QT correction methods rely on this assumption

Drug-related changes in the slope of QT-RR relationship create interpretation problems

Model-based QT corrections: Clinical trial example

Proof-of-concept study

Test drug induced heart rate changes

Mean heart rate increase, 8.8 bpm

Mean QTc change (Standard error)

Fridericia correction, 5.4 (4.5) msec

Population correction, 1.8 (4.4) msec

Model-based correction, 1.2 (4.0) msec

Individual correction (too few ECGs per subject)

Model-based QT corrections: Properties

Error rate control

Unlike fixed and population QT corrections, model-based method protects the error rate

Power

Model-based method is as powerful or more powerful than fixed and population QT corrections

Further reading

Population model-based corrections (Dmitrienko and Smith, 2003)

Individual model-based corrections (Ma, Smith and Dmitrienko, 2008)

QT corrections methods: General recommendations

Fixed methods

Unreliable

Population methods

Can be used in regular clinical studies

Individual methods

Recommended in thorough QT studies

Model-based methods

Recommended in regular and thorough QT studies (especially when heart rate changes are expected)

QTc-exposure analysis

QTc-exposure relationship

Characterization of QTc-exposure relationship is a key component of cardiac safety assessment

QTc-exposure analysis methods

No information in ICH E14

Topic has recently received much attention at conferences and in publications

QTc-exposure analysis: Objectives

Exploratory objective

Estimate shape of QTc-exposure relationship

Estimate QTc time course of in relation to plasma concentration levels

Evaluate QTc effects at low and high exposure levels

Confirmatory objective

Can QTc-exposure analysis be used for confirmatory purposes, e.g., define a negative thorough QT study?

QTc-exposure analysis: Details

Collection of PK samples

PK samples need to be collected at the time of ECG recordings

Critical to draw blood samples after taking ECG recordings

QTc-exposure analysis for positive control

It is becoming more common to collect PK samples for positive controls (moxifloxacin) (levetiracetam QT study)

Facilitate assay sensitivity analysis?

101

Module C

QTc-exposure analysis

QTc-exposure modeling

Linear model

Linear models are commonly used

$QTc \text{ change} = a + b C + \text{error}$

C, plasma concentration

Random subject terms is included if multiple ECGs per subject

Other models

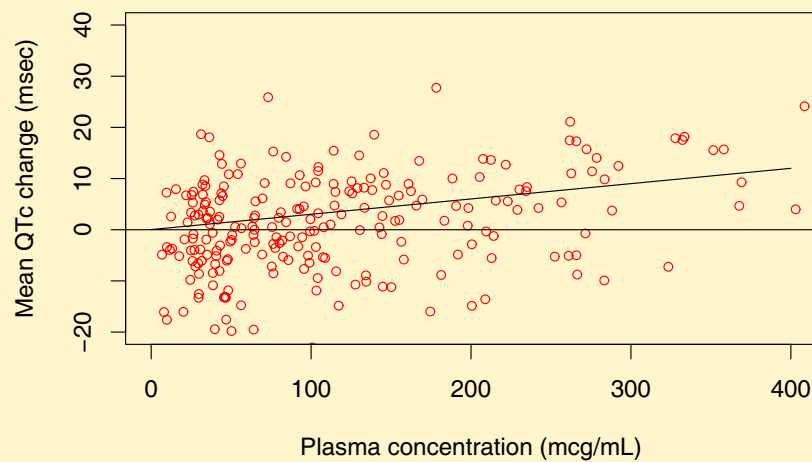
Non-linear models (e.g., sigmoid models) are rarely used although they make more scientific sense

102

Module C

QTc-exposure analysis

Linear QTc-exposure model



Assessment of QTc effects at therapeutic and supratherapeutic concentrations

103

Module C

QTc-exposure analysis

QTc-exposure modeling: Assumptions

Direct effect

Direct effect of the test drug's plasma concentration on QTc prolongation

Delayed effect

Pharmacodynamic t_{\max} occurs after pharmacokinetic t_{\max} (hysteresis of the QTc-concentration relationship)

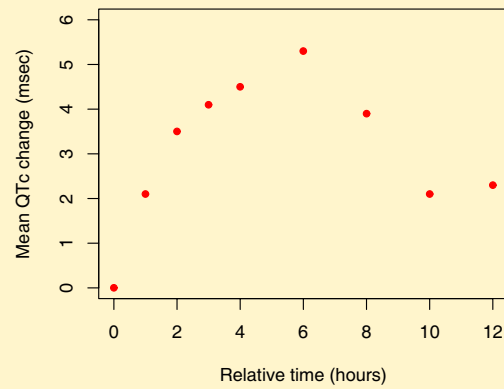
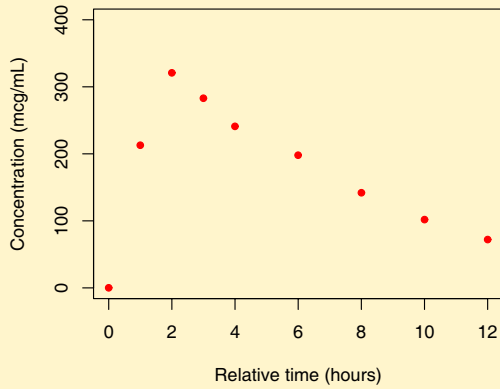
Peak QTc effect will be underestimated if hysteresis is observed

104

Module C

QTc-exposure analysis

Delayed QTc effect



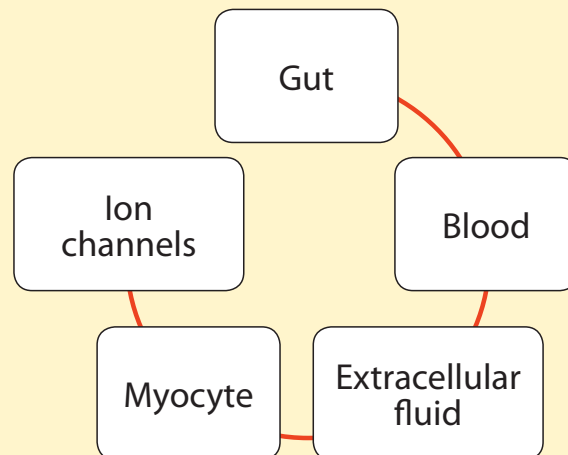
Peak plasma concentration at 2 h, peak QTc effect at 6 h

105

Module C

QTc-exposure analysis

Delayed QTc effect



From the gut to ion channels

106

Module C

QTc-exposure analysis

Delayed QTc-exposure relationship

How common is a delayed effect?

Drugs with a QTc prolongation potential tend to exhibit a delayed QTc effect (Dmitrienko, Beasley and Mitchell, 2008, Sec 4.4)

Indirect-response approach

Exposure-response models with a pharmacological effect compartment (e.g., Shi et al, 1995)

Sponsor can predict concentrations associated with the target QT effect

107

Module C

QTc-exposure analysis

QTc-exposure analysis: Estimation of QTc effect

Estimation of QTc effect in QTc-exposure analysis

Proposed by Garnett et al (2008)

Estimation procedure

Fit a linear QTc-exposure model

Construct a one-sided 95% confidence interval for mean QTc effect at mean C_{\max}

Decision rule

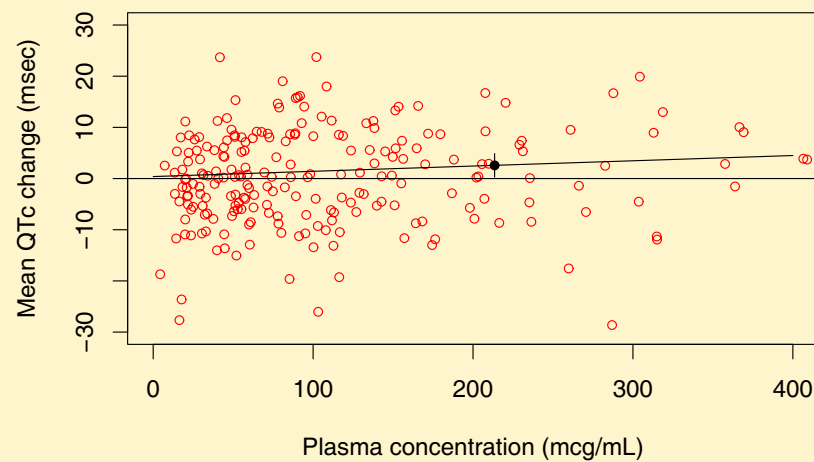
Compare the upper confidence limit to 10 msec

108

Module C

QTc-exposure analysis

Estimation of QTc effect



Mean QTc effect is estimated at mean C_{\max}
(upper confidence limit, 4.9 msec)

109

Module C

QTc-exposure analysis

Estimation of QTc effect: Example

Thorough QT study example (Garnett et al, 2008)

Comparison of moxifloxacin versus placebo

Traditional analysis

Point estimate, 14.5 msec

Upper confidence limit, 19.5 msec

QTc-exposure analysis

Point estimate, 12.5 msec

Upper confidence limit, 15.5 msec

110

Module C

QTc-exposure analysis

QTc-exposure analysis: Confirmatory objective

Properties

Important to better characterize statistical properties of this approach (Type I error rate, robustness, etc)

Assumptions

Direct QTc-exposure effect

Other assumptions

Further reading

Ring (2008)

Tsong et al (2008)