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Assessment of Concentration-QT Relationships in Pooled Phase 1 Studies using a real example

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Outline of the presentation

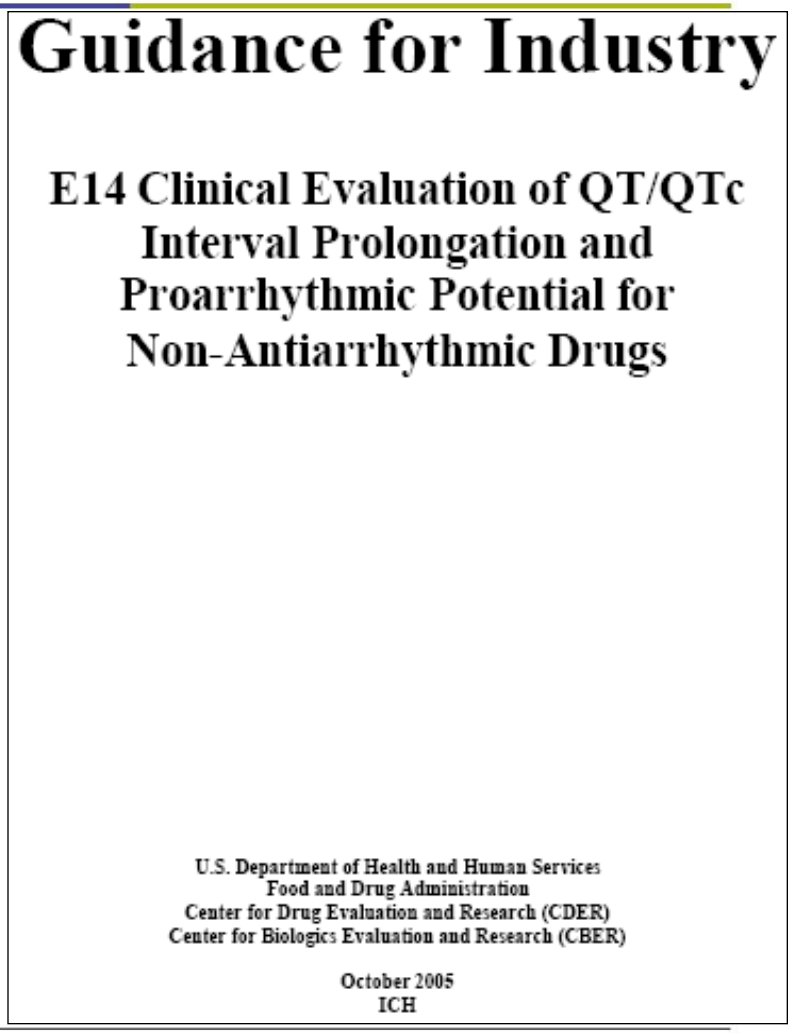
- Introduction
  - **ICH E14**
  - **New approaches**
- Application of new approaches to a real example
  1. **Population PK**
  2. **Modeling of the QT response**
- Discussion and conclusion

Rationale for thorough ECG studies

- Growing concern regarding deaths attributable to non-cardiovascular pharmaceutical agents
- Regulatory documents pertaining to the issue
  - **1997: European Medicines Evaluation Agency (EMEA)**
  - **2001: Health Canada**
  - **2002: US Food and Drug Administration (FDA)**
- Followed by initiation of the International Conference on Harmonization (ICH) process

Current guidance: ICH E14

- Born from a state of the art and scientific consensus
- Safety guide based on a pharmacodynamic method
- Intent is to provide guidance for clinical studies assessing the potential of a drug to delay cardiac repolarization
  - **Torsade de pointes (TdP)**



Objectives of thorough QT study

- Designed to enable detection of QT/QTc prolongation at the level of regulatory concern
  - **Mean effect on QT/QTc approximately 5ms**
  - **Upper 95% confidence interval exceeding 10ms**
- Generally applicable to all new agents
- Typically conducted early during clinical development
  - **Dictates future cardiac monitoring**
  - **Adequate knowledge of drug disposition**

Typical experimental plans of a TQT at Sanofi

- Double-blind/double dummy and randomization
- Crossover or parallel
  - **4 arms of treatment**
    - Placebo
    - IMP: 2 doses (therapeutic + supra-therapeutic)
    - Positive control (moxifloxacin)
    - Number of subjects ranging from 30 (crossover) to 60/group (parallel)
- Highly standardized procedures and conditions
  - **Decrease the variability**
- 24-h ECG profiles before and after treatment
  - **Covers the circadian rhythm or other variability of the parameter**
- Rich coincident PK sampling with ECG
  - **Allows a concentration-QT modeling**

C-QT modeling is encouraged

- « Regulatory review of a TQT study is **not complete without an assessment of the concentration-QT** relationship. »

  Norman Stockbridge, MD, PhD
  Director, Cardio-Renal Drug Products
  Interdisciplinary Review Team for QT
  CDER, FDA

- « For drugs that prolong QT, the approval and labeling decisions (eg, benefit-risk and dose selection) are based to a **large extent on dose- and concentration-QT** relationships. » (Garnett *et al*. J Clin Pharmacol. 2008;48:13-18)

  Christine Garnett, PharmD
  Scientific Lead
  Interdisciplinary Review Team for QT

- « Robust QT assessment (E-R analysis) in early phase clinical studies can replace a QT study. » Darpo *et al.* Clin Pharmacol Ther. 2015;97:326-35

  Results from the IQ-CSRC prospective Study support replacement of the Thorough QT study by QT assessment in the early clinical phase

Toward replacement of E14 guideline?

- Limitations of the ICH approach
  - **False positive**
  - **Lack of specificity**
  - **Precise information for prediction of proarrhythmic effects**

- Emerging effective alternative to TQT studies using routine early phase I
  - **Single (including FIM) and repeated dose studies**
  - **Intensive ECG monitoring (Holter)**
  - **No positive control arm (moxifloxacine)**
  - **Large dose range**
  - **Rich PK profile**
  - **Matching safety endpoints including ECG parameters**

Assessment of Concentration-QT Relationships in Pooled Phase 1 Studies Using a Real Example

Work performed in collaboration with Pharsight Consulting Services

The compound and phase I studies

- Orally-active urotensin II receptor antagonist (UTRA)
  - **Treatment of diabetic nephropathy**
  - **Urotensin has multiple effects on the cardiovascular and renal system and is vasoactive**

- The clinical development of UTRA has been terminated after two MAD studies
  - **Positive QT signal observed in both studies, among other reasons of termination**

- Studies
  - **Double blind, randomized, parallel-group, placebo-controlled, sequential ascending 14-day repeated-dose studies in healthy young male or elderly male and female subjects**
    - Study 1: 80 subjects (21 placebo, 61 active at 50, 130, 260, 350, and 500 mg UTRA)
    - Study 2: 36 subjects (12 placebo, 24 active at 50 and 260 mg UTRA)
  - **Administrations once daily with food**
  - **Triplicate ECGs extracted from Holter over a 24-hr period and centrally read (same ECG core lab) on Day -1 and Day 14**
  - **Full PK sampling on Day 1 and Day 14**

Objectives

- Develop a model to describe the population pharmacokinetics of UTRA in healthy subjects
- Develop population models to describe the relationship between UTRA plasma concentrations and QT endpoints in healthy subjects
- Quantify drug effect on QT prolongation for each dose
  - **Determine the dose threshold above which there is a QT signal**
- Define the probability that a patient receiving UTRA would show a QT prolongation

Support strategic decisions (Go/NoGo) early in the development

Methods - Population PK

- Model selection
  - **Guided by examination of model diagnostic plots**
  - **Changes in objective function**
  - **Precision of parameter estimates and lack of high correlations among them, symmetry of the distributions of individual parameter estimates about the estimated population parameter**
- Covariates
  - **Selected based on exploratory graphical and regression analyses**
  - **Sex, age, race and body size descriptors (body weight, BSA, LBW, IBW) on UTRA CL/F and Vc/F**
- At each stage of the analysis, the model was evaluated graphically and refined as necessary
  - **Adequacy of the final model and parameter estimates using the VPC method**

Methods - Concentration-QT modeling

- Endpoints
  - **3 QTcF endpoints considered**
    - Change from averaged baseline (ΔQTcFav)
    - Change from time-matched baseline (ΔQTcFtm)
    - Placebo-subtracted change from time-matched baseline (ΔΔQTcF)

  ➔The rest of the presentation will focus on ΔΔQTcF

  - **Concentration endpoint**
    - PK parameters from the Pop PK model (“Population C-QT approach”)

- A 4-step methodology
  - **Exploratory plots**
  - **Basic nonlinear mixed effects model: *ΔΔQTcF = Drug Effect + error***
    - Direct and delayed effect models explored
  - **Covariates tested: baseline QTcF, sex and age**
  - **Model assessment and qualification**

Methods - Simulation of QT prolongation

- Final population PK and C-QT models were simulated
  - **24 subjects were assigned to each dose group**
  - **35 sampling time points were simulated per subject (to capture the peak effect of the concentration)**

- Model-predicted ΔΔQTcF estimate simulated (1000 study replicates) by simulating *Drug effect*
  - **5^{th}, 50^{th} and 95^{th} percentiles calculated at each time point & plotted**
  - **Median ΔΔQTcF calculated at the median peak plasma ("effect-site") concentration (Ce,max)**
  - **Probability of a 10 msec-change in median ΔΔQTcF calculated at each dose**
    - Number of replicates with median response greater than 10 msec as a fraction of the total number of replicates

Methods - Softwares

- Data manipulations, statistical and graphical exploratory analyses, and post-processing and graphical presentation of results were completed within the R and S-PLUS™ environments

- Population pharmacokinetic analyses, C-QT analyses and simulations were performed within NONMEM™ (version VII)

- Analyses using NONMEM were run using the first order conditional estimation with interaction (FOCE INTERACTION) method

Data overview

- Summary of subjects and observations used in the PK and C-QT analyses

Study #	Doses (mg)	No. Subjects per Treatment	Mean age % males	Total No. Subjects: PK/CQT	Total No. PK Observations	Total No. ΔΔQTcF Observations
1	placebo, 50, 130, 260, 350, 500	20 (placebo) else 12	30 y.o. 100%	60/80	2220	577
2	placebo, 50, 260	12	68.7 y.o. 33%	24/36	888	239
Pool	placebo, 50, 130, 260, 350, 500	32, 24, 12, 24, 12, 12	42.5 y.o. 78%	84/116	3108 (37/subject*)	816 (7.0/subject*)

** Average number of observations per subject*

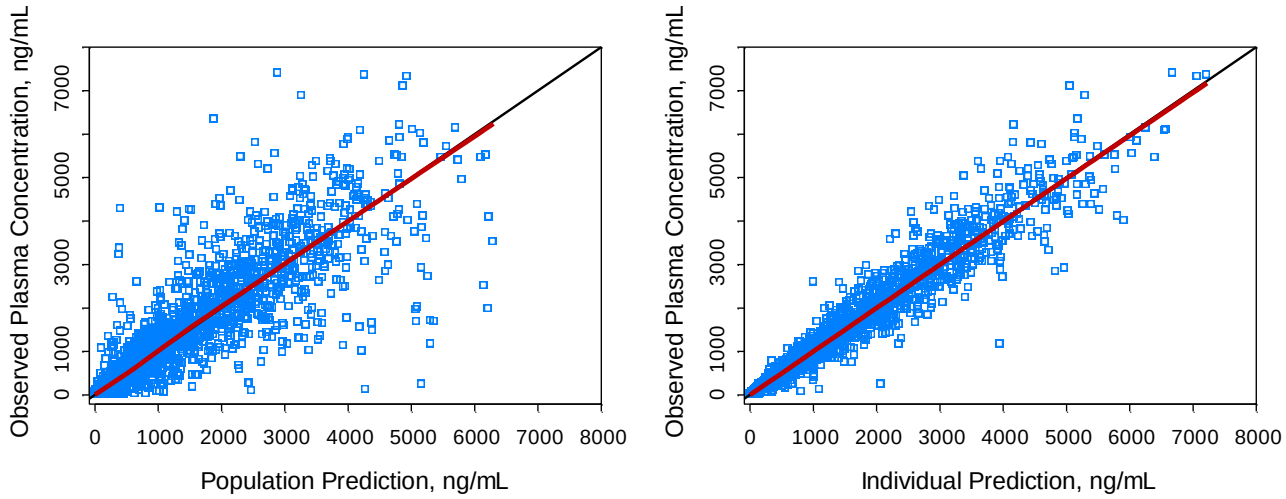
Results - Population PK

- Sequential structural model development approach
  1. **A 2-compartment mammillary PK model with delayed first order absorption of drug from an oral dosing compartment described the PK of UTRA**
  2. **A simple absorption model including first order absorption with a lag time provided a good fit to the data**
  3. **A modified transit compartment model best fitted the data**
     - absorption rate constant (Ka) was constrained to equal the transit rate constant (Ktr)
     - reduction in AIC of 600 points compared to lag model
     - better capture of peak plasma concentrations
     - residual variability was described using additive and proportional error terms

Results - Population PK

- Evaluation of covariate effects
  - **Significant relationships between body surface area and both apparent clearance (CL/F) and apparent volume of the central compartment (Vc/F)**
    - effects of BSA were such that heavier subjects were estimated to have larger Vc/F and faster CL/F

- Model assessment showed that the population PK model performed well with clear concordance between observed data and individual model predictions



Goodness of fit plots for final model

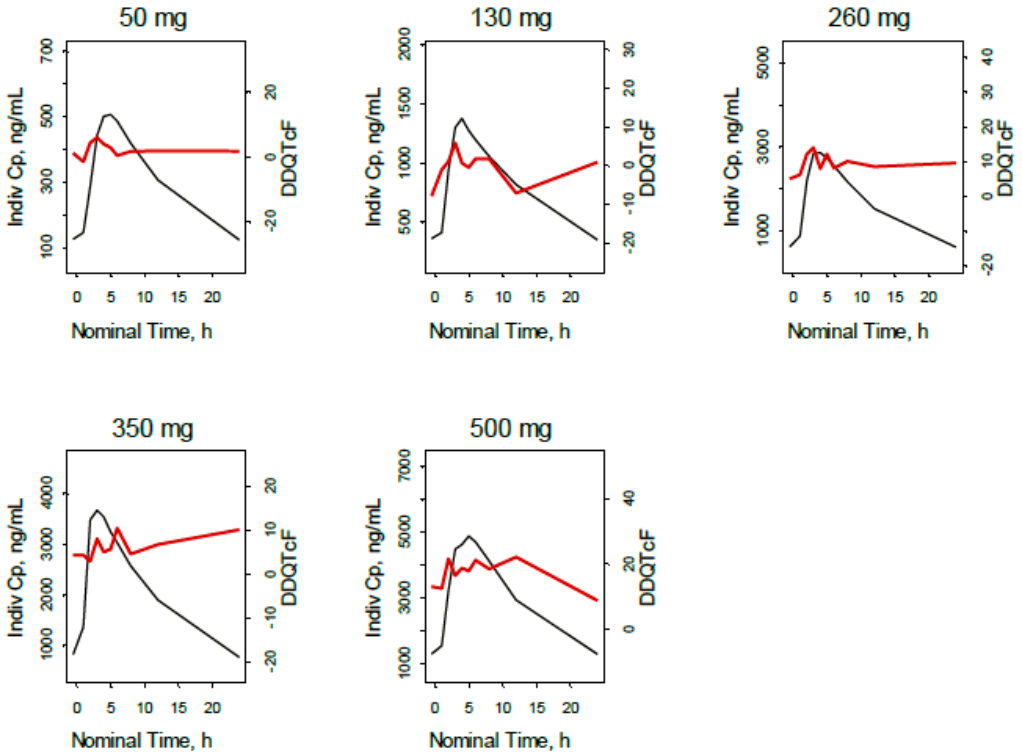
Circles represent observations , black line represents unity , red line represents a smoothing function

Results - Population PK

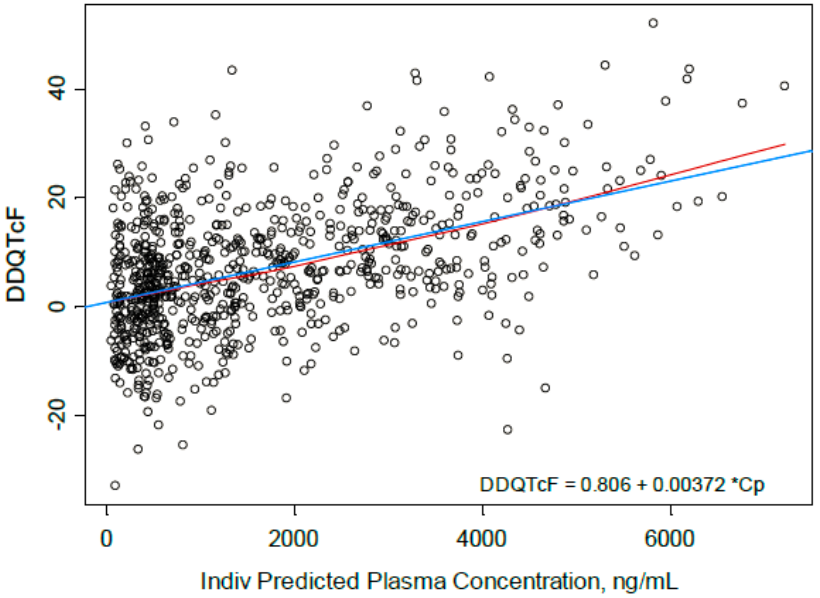
- Parameter estimates for the final population PK model

Population PK Parameter	Units	Typical Value (%RSE)	%IIV (%RSE)	Shrinkage (%)
CL/F	L/h	7.5 (2.5)	19.9 (18.8)	1.4
Vc/F	L	91.3 (2.1)	15.6 (23.6)	10.3
Q/F	L/h	1.53 (15)	NE	NE
Vp/F	L	19.2 (11)	52 (27.9)	7.7
MTT	h	0.938 (6.1)	58.2 (14)	8.1
N		1.94 (12.1)	NE	NE
Ktr	1/h	3.1	-	-
BSA on CL/F		1.4 (16.2)	-	-
BSA on Vc/F		1.91 (9)	-	-
Correlation CL/F - Vc/F		0.749 (7.6)	-	-
IOV - MTT	%	58.2 (14)	-	4.4
Residual Error - proportional	%	21.4 (9.6)	-	6.1
- additive	ng/mL	1.05 (56.5)	-	6.1
OFV		30522.298		

Results – Exploratory C-QT plots



Median predicted plasma concentration (in black) and median observed ΔΔQTcF (in red) over time by dose



Circles are observations, red line is a smoothing function and blue line is a linear regression (equation shown)

- **QT peak at T5h for all dose groups**
- **Clear linear relationship between QT endpoints & predicted concentration**
- **Evidence of a delayed drug effect ➔ taken into account in the model**

Results - Concentration QT modeling

- Final model

$$\Delta\Delta QTcF_{ij} = DrugEff_i + \eta_{1i} + \varepsilon_{ij}$$

$$Ke0_i = Ke0_{TV}$$

$$dCe/dT = Ke0_i*(Cp_{ij} - Ce_{ij})$$

$$DrugEff_i = slope_{TV} * Ce_{ij}$$

i=subject, j=observation, TV represents typical population value

Ke0 is the transfer rate constant between plasma and the hypothetical effect compartment which defines the delay in drug effect

Cp and Ce: plasma concentration and effect site concentration

Interindividual variability in placebo response (η_{1i}) was normally distributed with mean of 0 and variance of ω^2

ε_{ij}: residual variability, modeled as a normally distributed variable with mean of 0 and variance of σ^2

Results - Concentration QT modeling

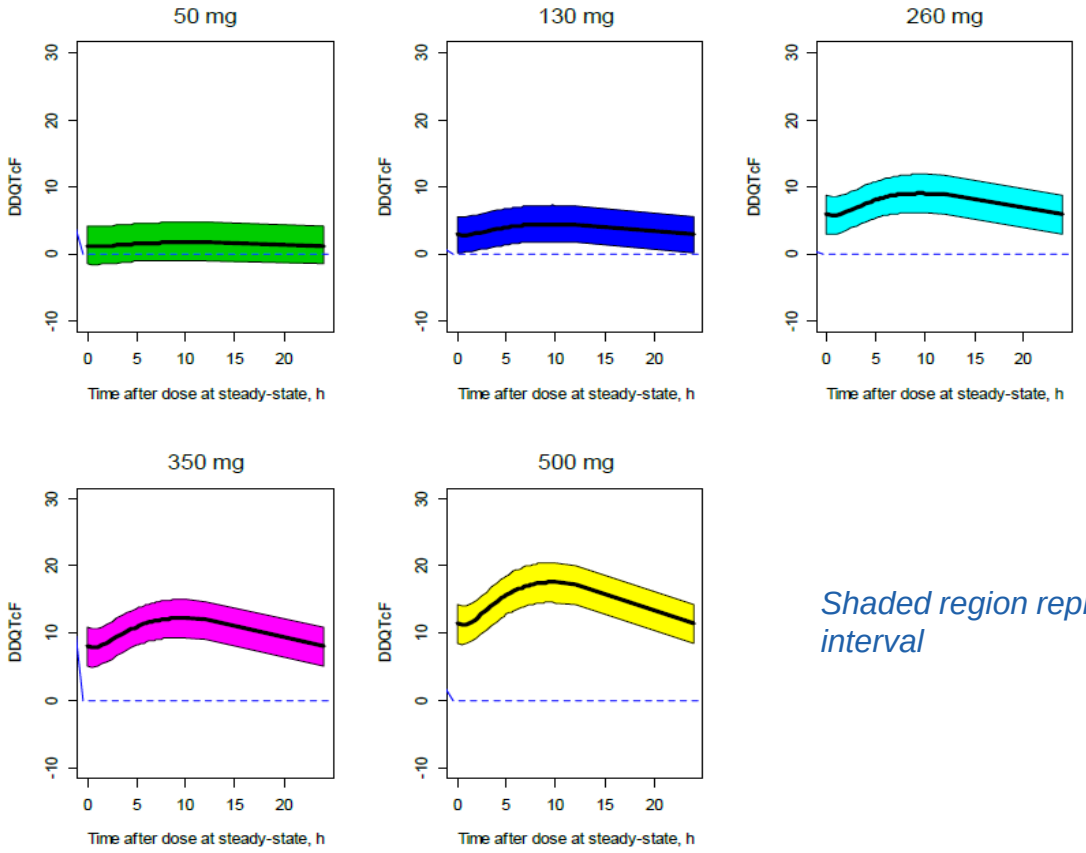
- Parameter estimates for the final model

Parameter (unit)	Estimate	Relative standard error (%)	Variability	Shrinkage
Drug effect model				
$Slope_{TV}$ (msec/ng/mL)	0.00535	12.3		
$Ke0_{TV}$ (h^{-1})	0.0953	61.3		
Interindividual variability				
ΔΔQTcF (additive) (msec)	43.5	22.3	6.6	6.5
Residual variability				
Sigma (additive) (msec)	65.5	7.1	8.1	4.6

- Model diagnostic plots ➔ data described adequately by the model
- Impact of covariates: no effect of sex, age or baseline QTcF on inter-subject variability in ΔΔQTcF

Results - Simulation of QT prolongation

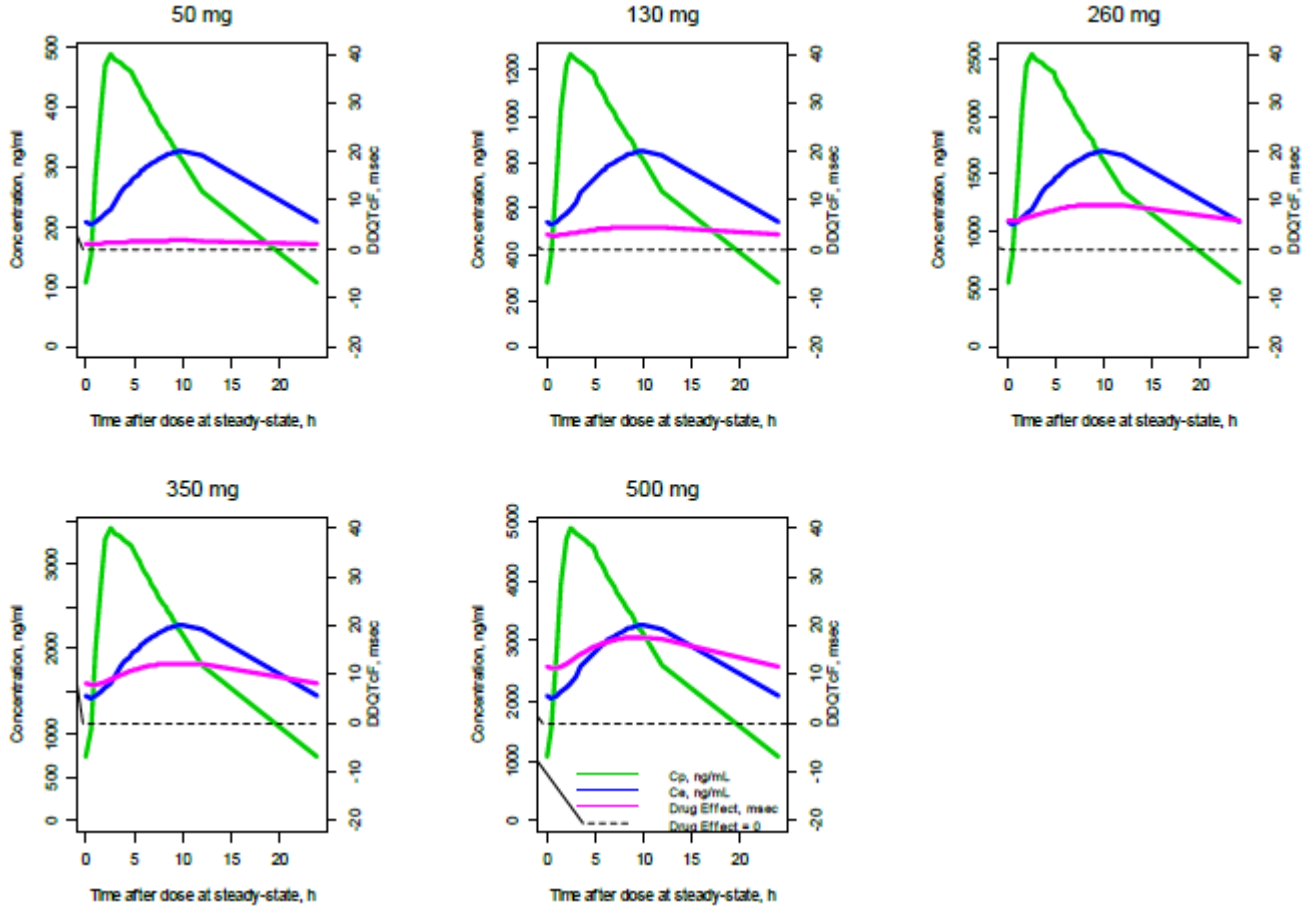
- 1000 studies replicated
- Simulated median ΔΔQTcF prolongation profile by dose:



Shaded region represents 90% prediction interval

Results - Simulation of QT prolongation

- Median of 1000 simulated study replicates showing plasma concentration (green), effect site concentration (blue) and QT prolongation (pink) over time by dose for ΔΔQTcF CQT model



Results - Simulation of QT prolongation

- Probability of median ΔΔQTcF at Ce,max > 10 msec calculated at each dose

Dose (mg)	Median Ce,max	Drug effect at Ce,max			Probability of QT prolongation > 10 msec
		5%	50%	95%	
50	327.95	-0.89	1.77	4.77	0
130	851.74	1.88	4.51	7.31	0.1
260	1703.50	6.27	9.13	11.96	29.7
350	2293.10	9.40	12.28	15.03	91.0
500	3275.95	14.63	17.63	20.55	100

- **Little risk of QT prolongation for doses 50 & 100 mg; high risk for 350 & 500 mg**
- **At 260 mg: 30% of subjects are expected to show QT prolongation, even if median drug effect was lower than 10 msec (IIV: SD=6.6 msec)**

Conclusions (1/2)

- A population pharmacokinetic and C-QT analyses for UTRA using data collected in two Phase I studies was implemented

- UTRA pharmacokinetics were ascribed a 2-compartment open model
  - **The "transit" model provided a better description of the delay in absorption than the "lag" model**
  - **The most significant covariate was BSA**

- A nonlinear mixed-effects modeling approach was successfully implemented to describe ΔΔQTcF
- A delayed linear drug effect model adequately described C-QT relationships
- No effect of the covariates tested (despite large interindividual variability)

Conclusions (2/2)

- Based on simulation of the drug effect term of the C-QT model
  - **350 and 500 mg doses were expected to produce median ΔΔQTcF prolongations at peak effect site greater than 10 msec**
  - **260 mg dose might not be entirely safe according to simulations: 30% of subjects were expected to have QT prolongation > 10 msec due to interindividual variability in drug response, even if median QT prolongation at peak effect was lower than 10 msec**
  - **Only 50 and 130 mg doses were safe in regards to QT prolongation**

- This work also enabled us to
  - **Compare 3 different QTc endpoints/baselines, and thus could be used for internal decision**
  - **Confirm clinical ECG findings observed in each study**
  - **Quantify the risk of QTc prolongation in each dose in a simple way**

Perspectives

- Science
  - **Knowledge of cardiovascular safety profile of new compounds**
  - **Exploit thoroughly the phase I data**
  - **Solid simulations**
- Development strategy
  - **“Use the concept” to help for internal Go – NoGo decisions early in development**
  - **Identify safe and at risk doses**
  - **Rationalize development**
    - Delay investments (TQT study, ECG monitoring in Ph2/3)
    - Save time and money
- Regulatory acceptability
  - **Substitute to a TQT study**

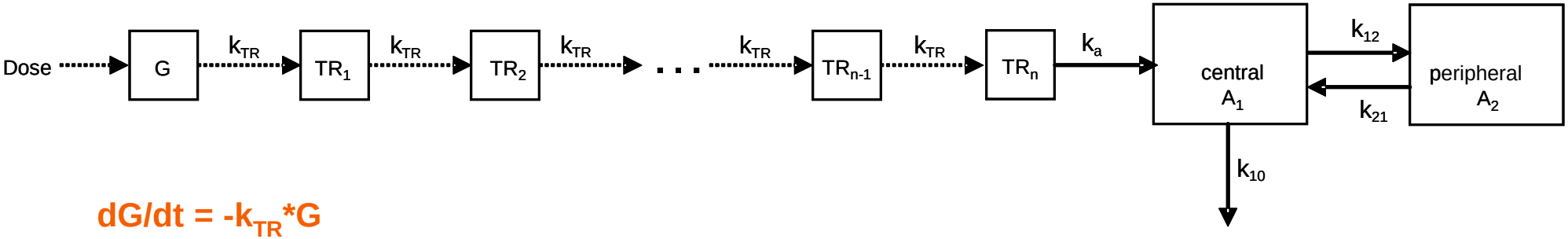
Acknowledgements

- Pharsight: Helen Kastrissios & Christine Garnett
- Sanofi: Catherine Ortemann-Renon (CEP), Bernard Sébastien & Franck Poitiers (B&P), Quyen Nguyen (DSAR DD)

Back up

Schematic PK model

- 2-compartments model, Transit



$dG/dt = -k_{TR}*G$

$dTR_1/dt = k_{TR}*G - k_{TR}*TR_1$

...

$dTR_n/dt = k_{TR}*TR_{n-1} - k_a*TR_n$

$dA_1/dt = k_a*TR_n - k_{10}*A_1 - k_{12}*A_1 + k_{21}*A_2$

$dA_2/dt = k_{12}*A_1 - k_{21}*A_2$

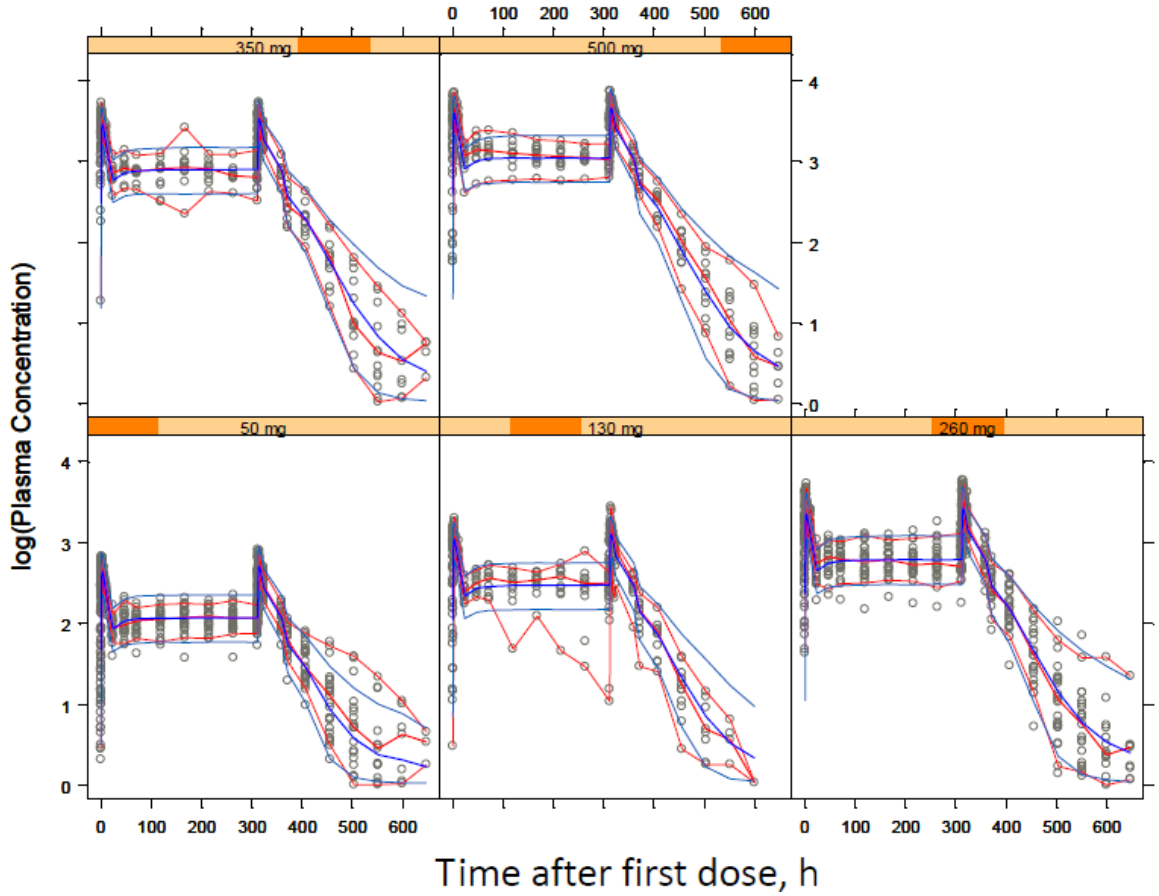
Number of transit compartments: $n = Mtt * k_{TR}$

Mtt: mean transit time

Savic, 2007

Results - Population PK

- Visual predictive check for final model : all doses
  - **Red lines represent median and 90% CI of observations, blue lines represent median and 90% prediction interval (PI) for 400 simulations of the final PPK model. Circles represent observations**



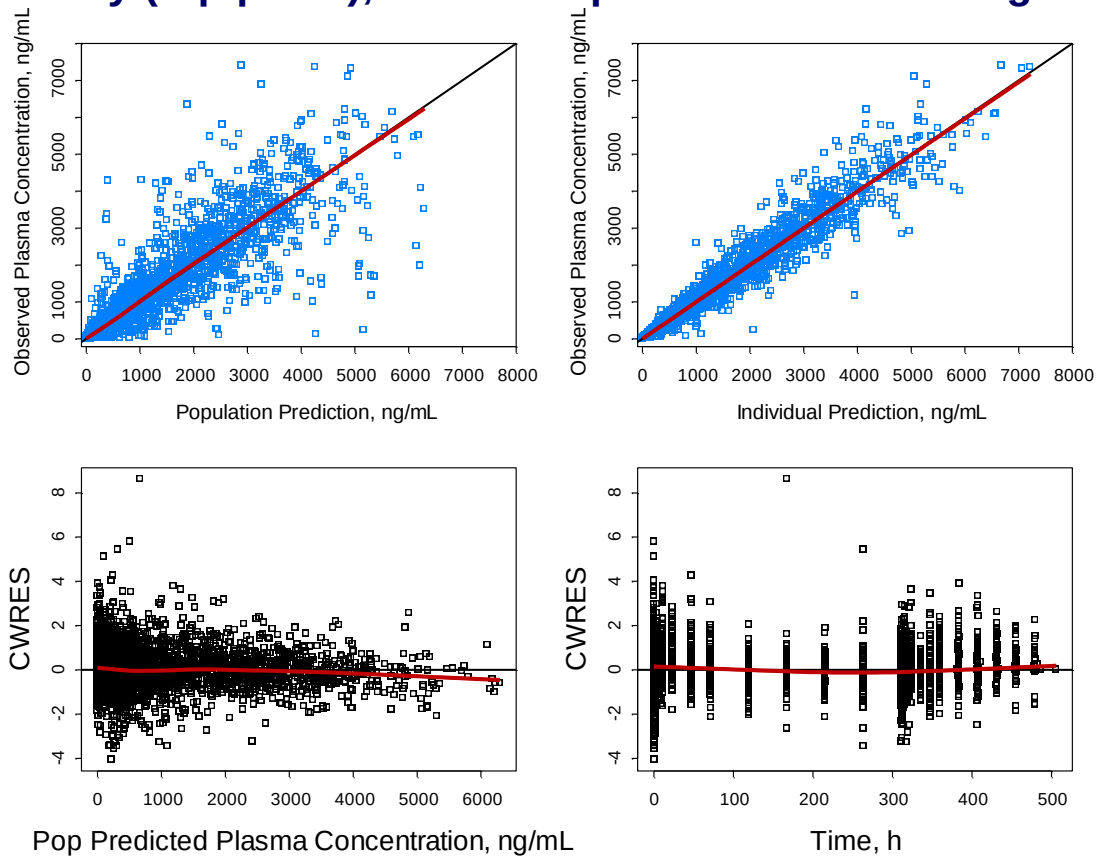
Results - Population PK

- Effect of BSA on drug exposure
  - **For a 260 mg dose, a 56% increase in BSA from 1.4 m² to 2.2 m² is predicted to result in a median 47% decrease in AUC,ss**

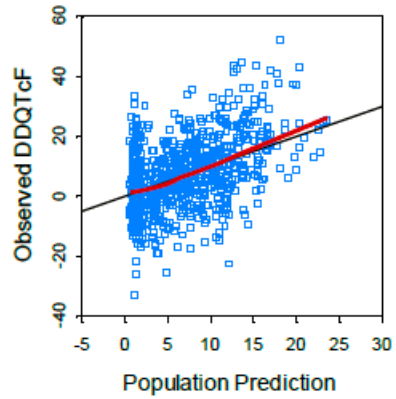
BSA m^2	CL/F L/h	Vc/F L	AUC,ss for 260 mg mg.h/L
1.4	4.89	51.0	53.2
1.9	7.50	91.3	34.7
2.2	9.21	120.8	28.2

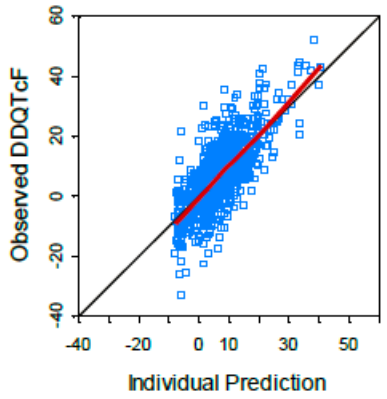
Diagnostic plots for POP PK modeling

- Goodness of fit plots for final model
  - **Circles represent observations (top panel) or residuals (bottom panel), black line represents unity (top panel), red line represents a smoothing function**

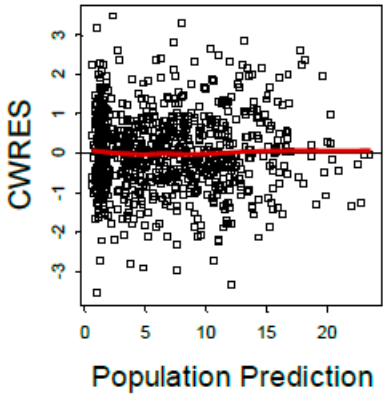


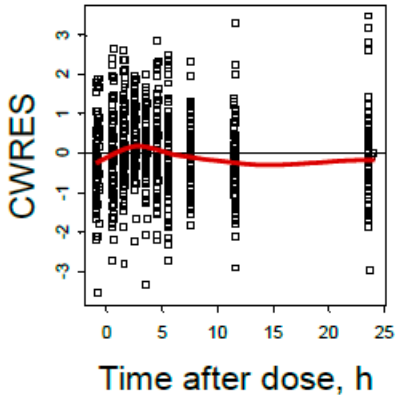
Goodness of fits plots for C-QT modeling





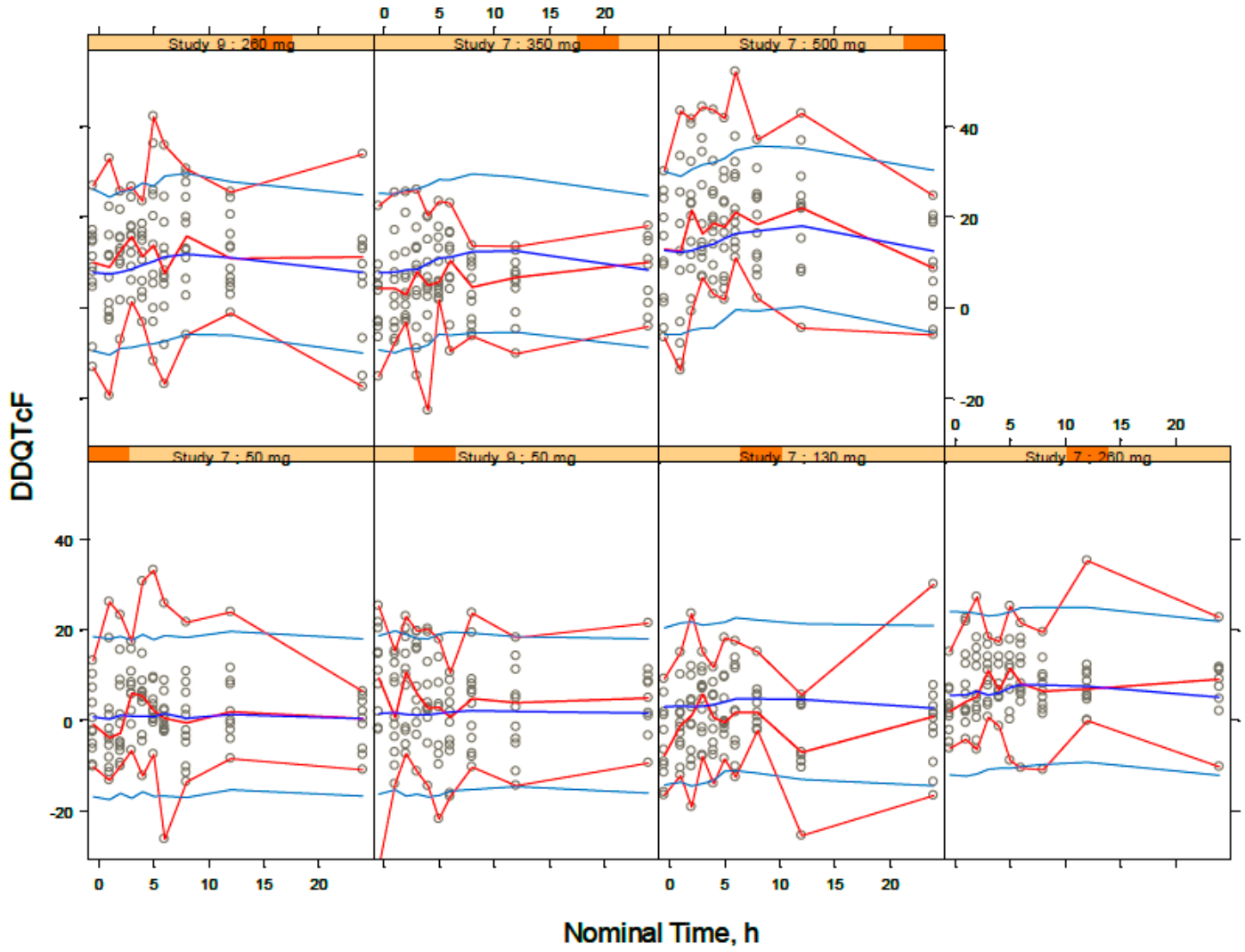
Circles are observations; black line represents unity; red line represents a smoothing function





Squares are observations; red line represents a smoothing function.

Visual predicted checks for C-QT final model



Red lines represent median and 90% CI of observations, blue lines represent median and 90% prediction interval (PI) for 100 simulations of the final of ΔΔQTcF CQT model. Circles represent observations