Pharmacokinetic–Pharmacodynamic modeling to assess the relationship between a New Molecular Entity (NME) treatment and QT/QTc interval prolongation

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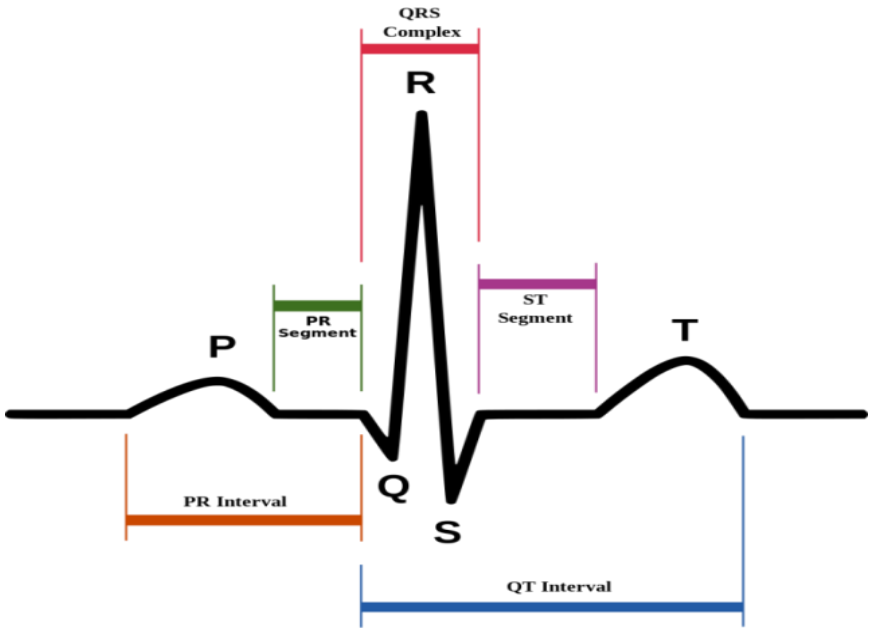
Outline

- Background
- Study Design
- QT/QTc Modeling
- PKPD Model Development
- Simulation of QT/QTc
- Discussion - Limits

Background

- QT interval : QRS Complex/T-wave



- Drugs can significantly prolong QT interval of ECG
- Potential life threatening risk (“Torsades de Pointes”)

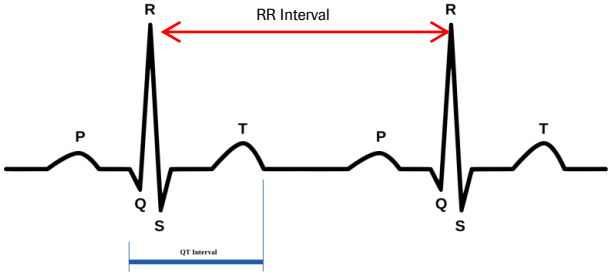
Background

- NME is currently in Phase II
- No signal of QT prolongation in preclinical studies
- No clear signal of QT prolongation from completed studies
- But small increase in QT interval at supra-therapeutic exposures cannot be excluded
- Assessment of the QT-prolongation risk for go/no-go decision for further development of the molecule before the beginning of Phase III on target population

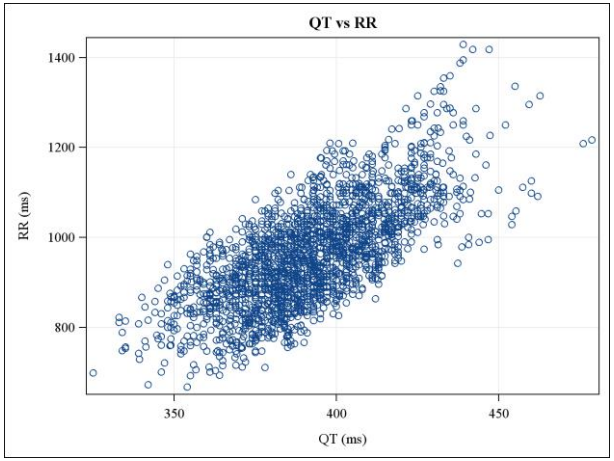
Study Design

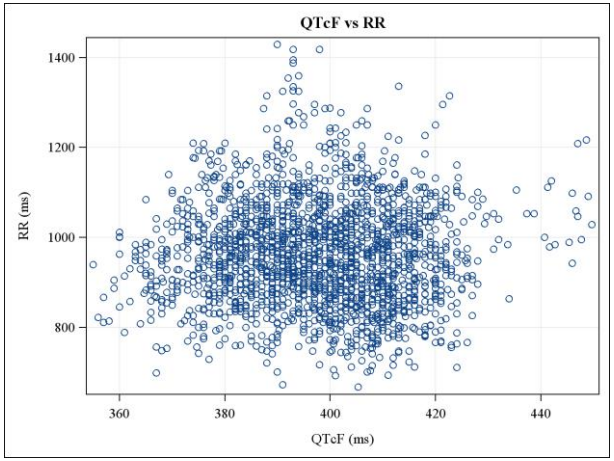
- 1 SAD study and 2 MAD studies
- Phase I randomized, double-blind, placebo-controlled
- 128 Male Healthy Volunteers
- 15 different doses + placebo treatments
- Full PK Profile : D1, D8, D10, D13, D20
- ECG Measurement : BL, D1, D2, D4, D7, D10, D13, D20

QT/QTc Modeling



- RR Interval
- Fridericia Correction : $QTcF = QT \times RR^{-0.33}$





- Individualized Correction : $QTc = QT \times RR^{\alpha}$
- Circadian Rhythm : daily variations

$$QT = MES \bullet \left(\frac{RR}{1000}\right)^{\alpha} \bullet \left(1 + Amp_{12h} \cdot \cos\left(2\pi \frac{time - Acr_{12h}}{12}\right) + Amp_{24h} \cdot \cos\left(2\pi \frac{time - Acr_{24h}}{24}\right)\right)$$

PKPD Model Development for QT

- Use of observed PK Concentration QT relationship approach
- Data suggested no placebo effect
- Various circadian rhythms were tested: 1 to 3 cycles with different periods
- Various drug effect models were tested: linear, power, Emax, Sigmoid Emax
- Graphical investigation of age and BMI on PD parameters
- BSV were evaluated on all PKPD parameters
- Residual error described by an additive error model

PKPD Model Development for QT
Final Model with J-shaped drug effect

$$QT = \underbrace{MES \bullet \left(\frac{RR}{1000}\right)^{\alpha} \bullet \left(1 + Amp_{6h} \cdot \cos\left(2\pi \frac{time - Acr_{6h}}{6}\right) + Amp_{24h} \cdot \cos\left(2\pi \frac{time - Acr_{24h}}{24}\right)\right)}_{\text{Baseline}} + DrugEffect$$

Parameters	Unit	Estimate	RSE (%)
Fixed Effect Parameters			
θ_1 Mes	ms	399	0.3
θ_2 α	-	0.284	1.7
θ_3 Amp6	-	0.00362	12.0
θ_4 Arc6	h	3.40	3.6
θ_5 Amp24	-	0.00896	8.9
θ_6 Acr24	h	3.53	4.9
θ_7 Slope1	ms.mL/ng	-0.0139	14.4
θ_8 Slope2	ms.mL/ng	0.000641	22.7
θ_9 Threshold	ng/mL	279	12.4
Random Effect Parameters			
ω_1^2 BSV on Mes	% CV	3.9	23.1
ω_2^2 BSV on α	% CV	12.1	12.3
ω_4^2 BSV on Acr6	% CV	30.7	20.7
ω_6^2 BSV on Acr24	% CV	35.5	43.5
ω_7^2 BSV on Slope1	% CV	103.5	28.3
θ_{10} Additive residual error	ms	5.01	1.8
OFV: 17897.53			

- If Cp≤279 mL:

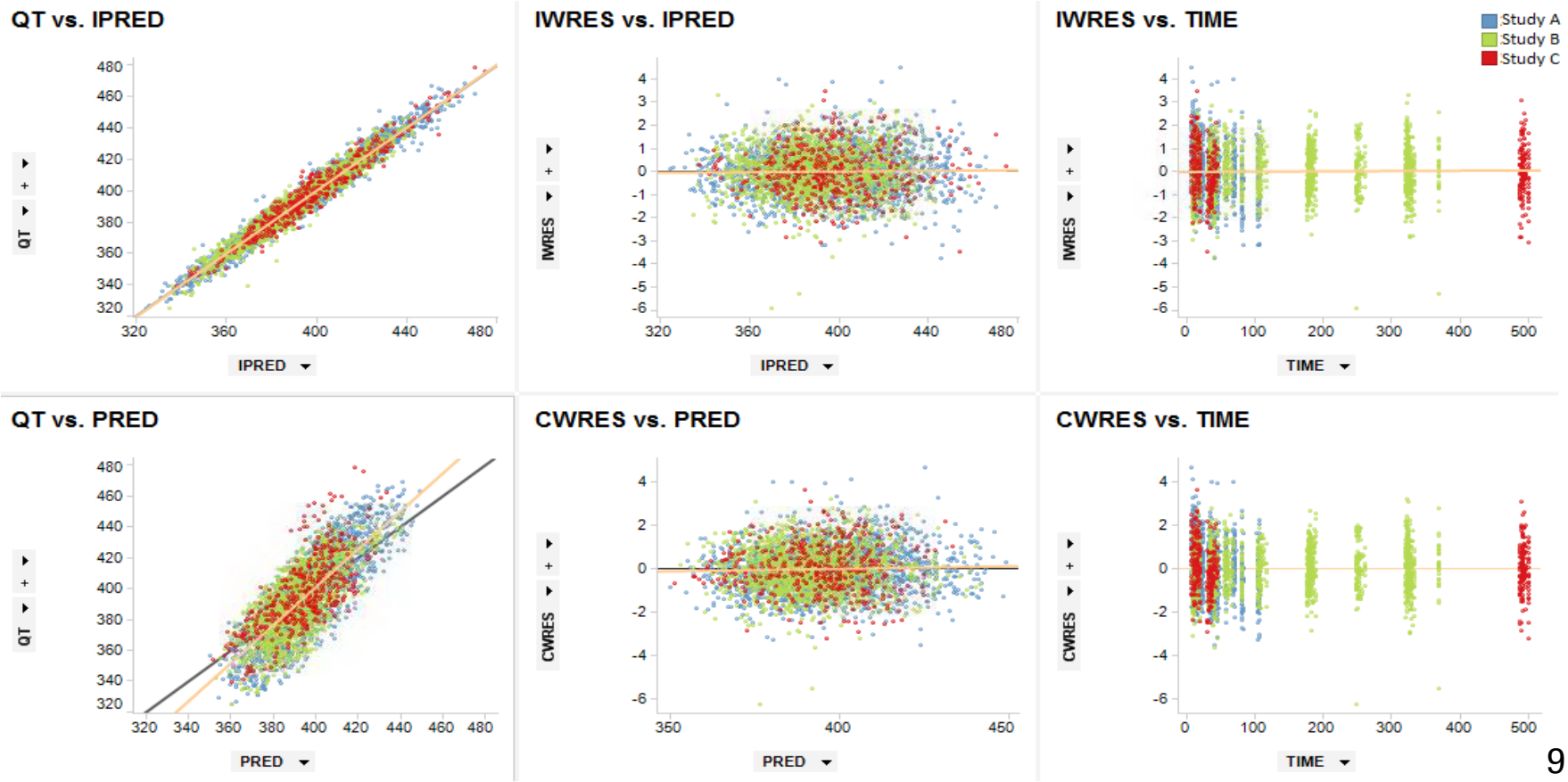
$$DrugEffect = Slope1 \times Cp$$

- If Cp>279 mL:

$$DrugEffect = Slope2 \times Cp - (Slope1 - Slope2) \times 279$$

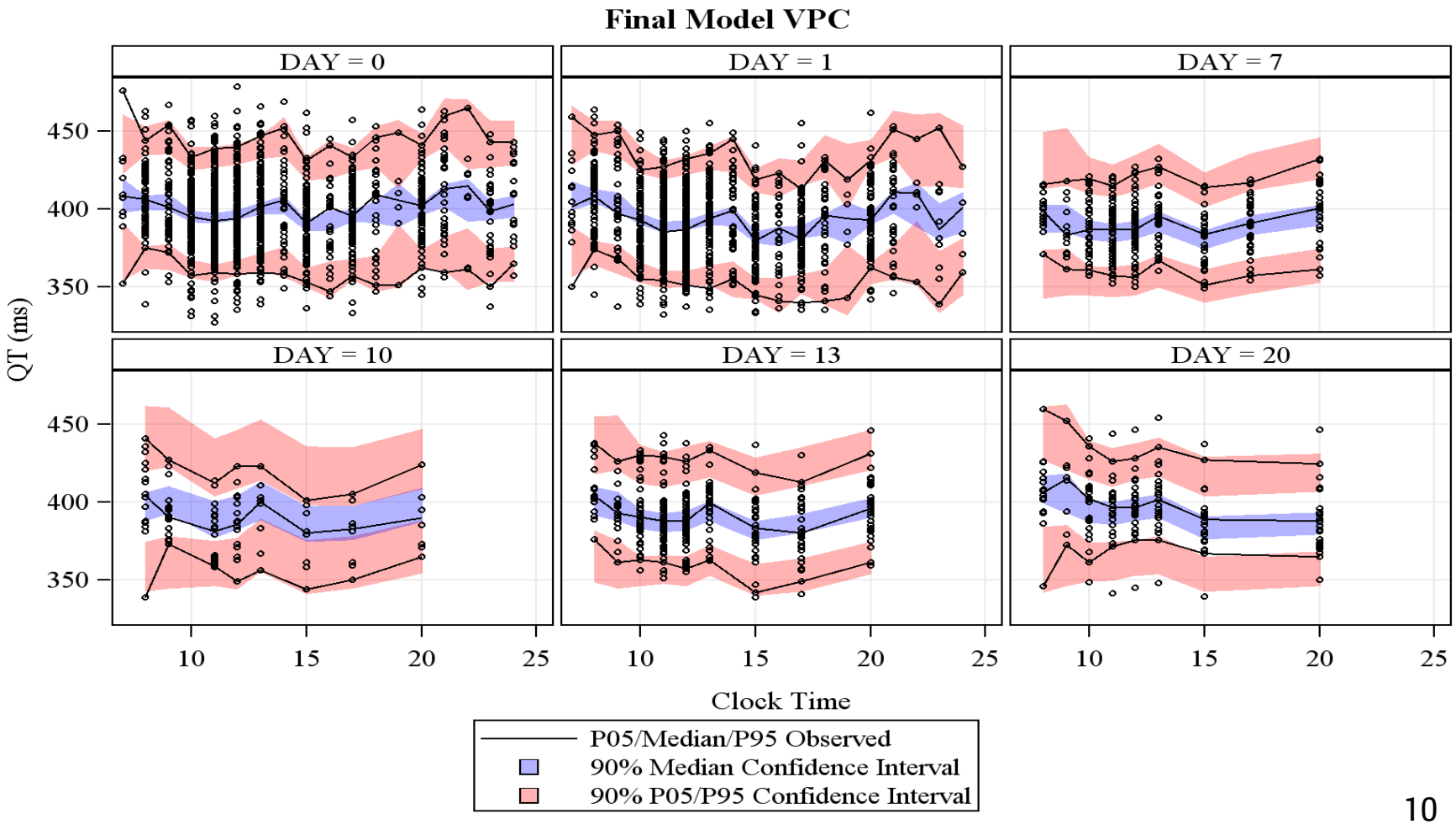
PKPD Model Development for QT
Goodness of fit plots

- Slight Biais on Population Predictions
- Good Individual Predictions



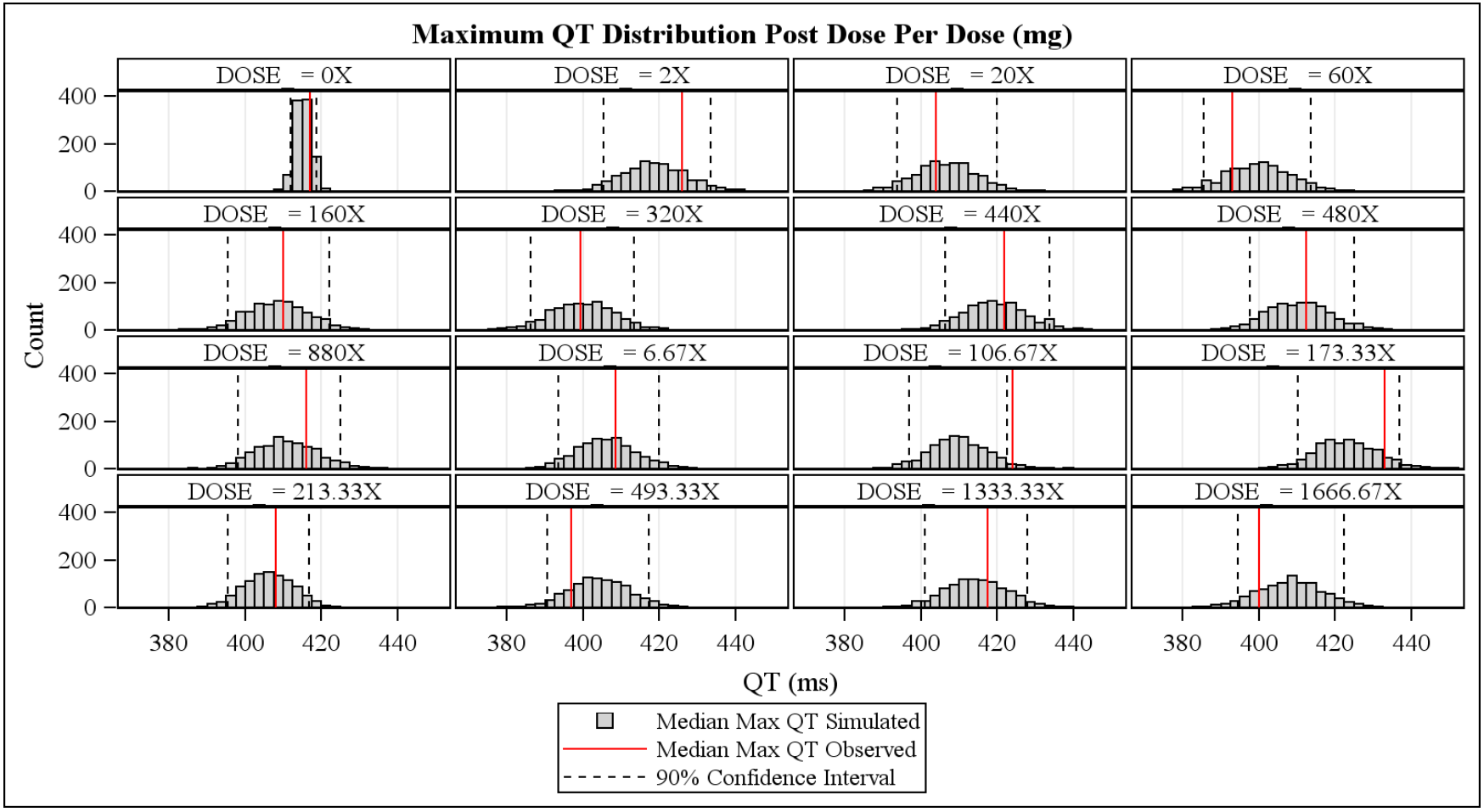
PKPD Model Development for QT
Visual Predictive Check (VPC)

- Model describes adequately the variability in the data



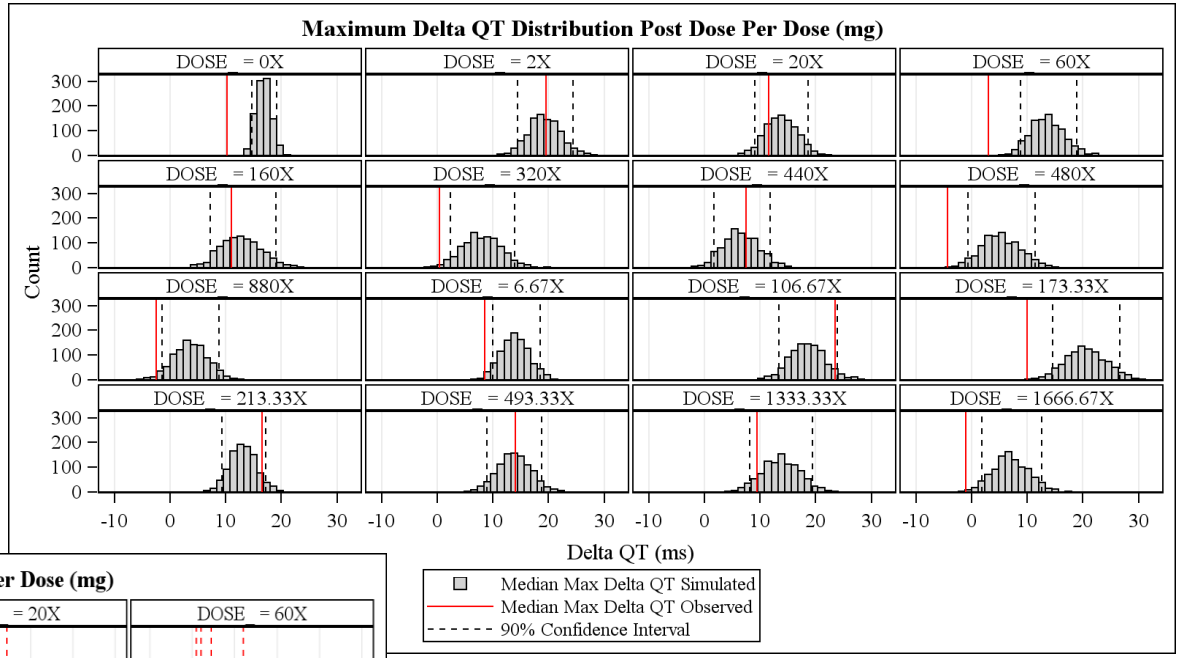
PKPD Model Development for QT Posterior Predictive Check (PPC)

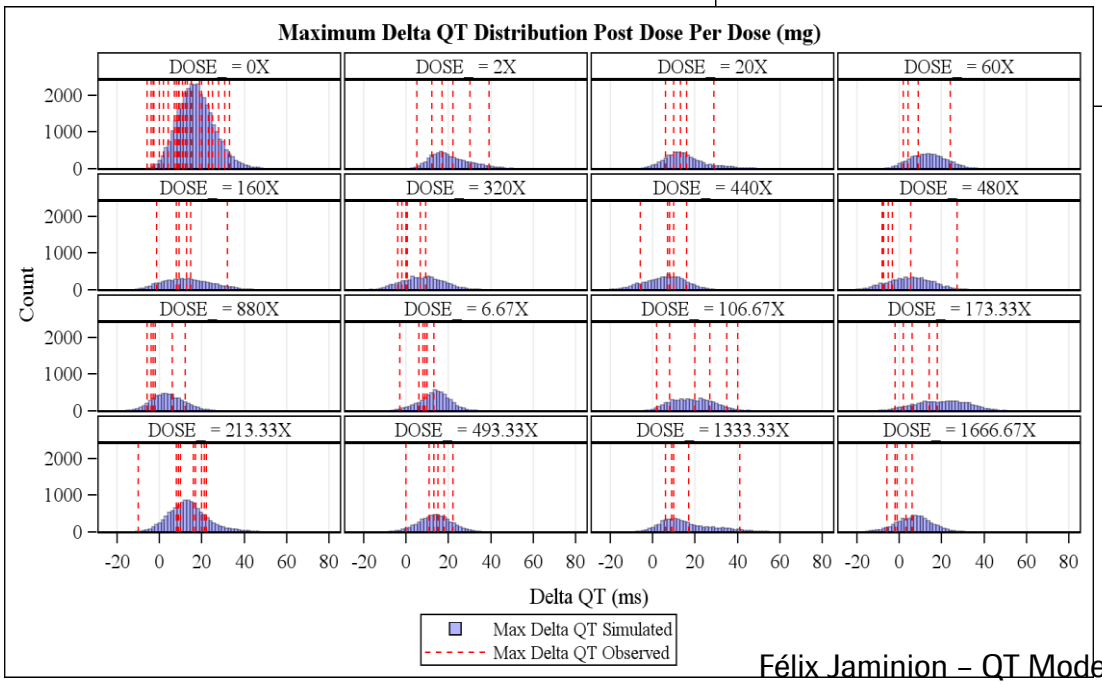
- Simulated data match with observed data



PKPD Model Development for QT Model Qualification

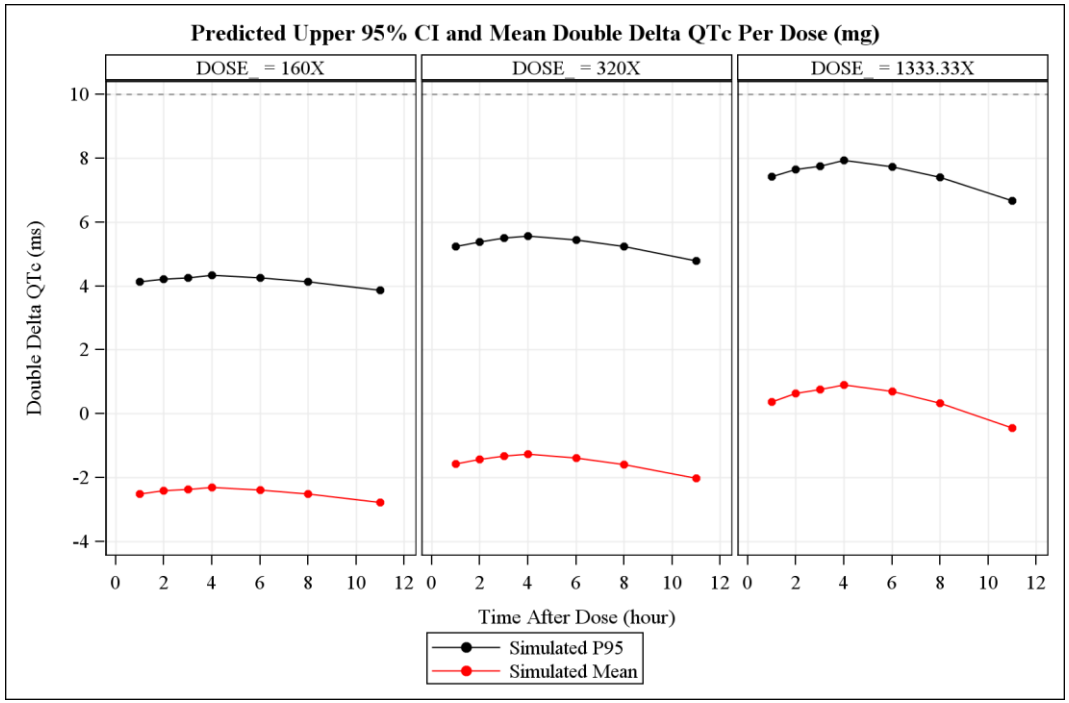
- ΔQT – Time-Matched Change From Basline
- Only 6 patients per dose





Simulation of QTc at Steady State

- Magnitude of the drug effect on QT prolongation is unlikely to be of clinical concern, even at high exposure



Dose	QTc (ms) > 480 (%)	QTc (ms) > 450 (%)	ΔQTc (ms) > 30 (%)	ΔΔQTc (ms) > 10 (%)
160X mg	0.02	0.89	0	0.1
320X mg	0.02	0.9	0	0.25
1333.33X mg	0.03	1.13	0	1.32

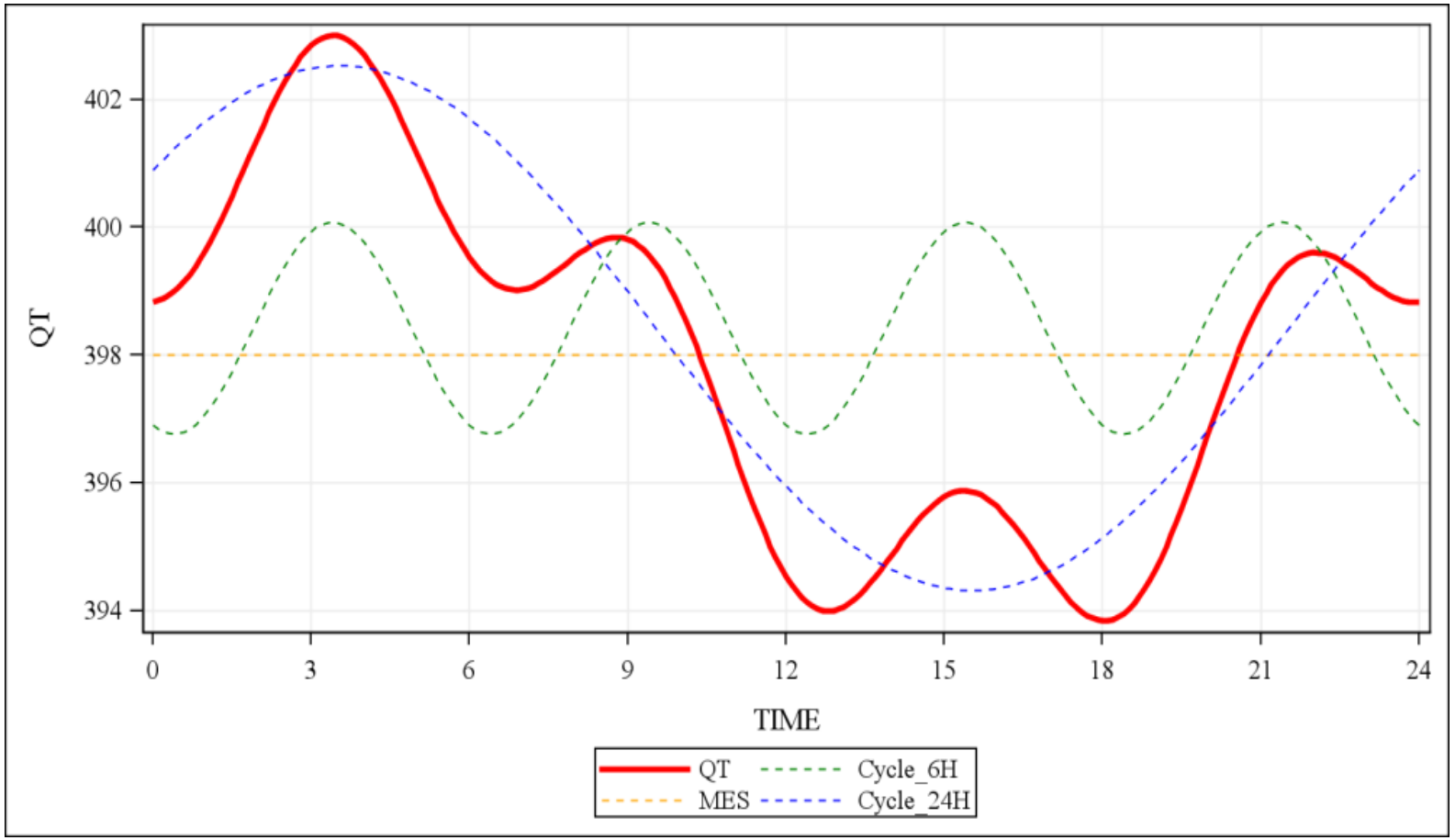
Discussion

- Exploratory QT provides an assessment of QT prolongation risk
- J-shaped drug effect
  - Shorten QT interval with Cp ≤ 279 ng/mL
  - Prolong QT interval with Cp > 279 ng/mL
- Simulations on 3 different dosing groups
  - No ΔQTc above 30 ms
  - ΔΔQTc 95% upper bound confidence interval < 10 ms
- Weak drug effect with no clinical concern even at high exposures
- Limits
  - No PK model explaining the SAD and MAD exposures simultaneously
  - Concentration QT modeling approach only uses time-matched PK QT data

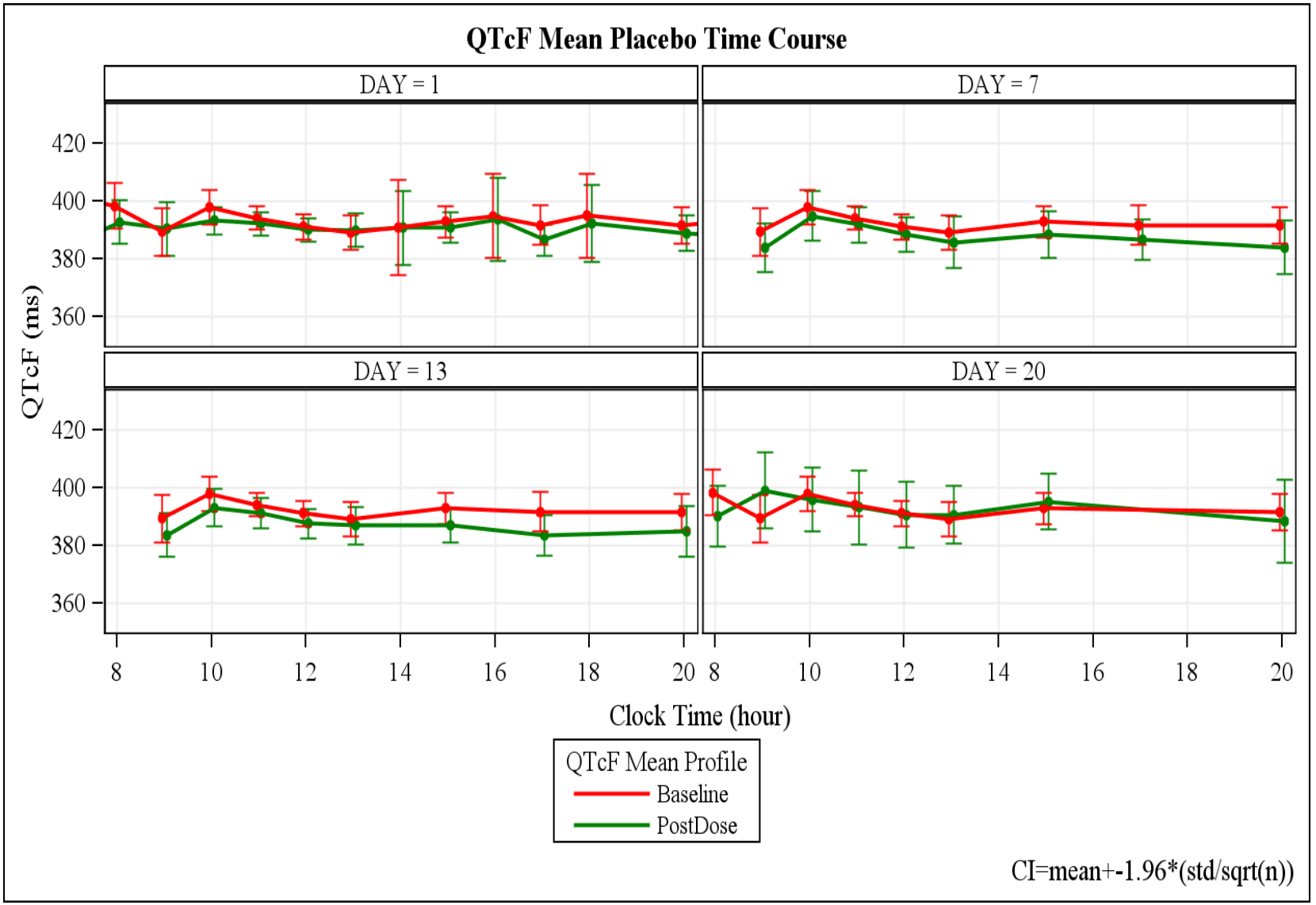
Merci de votre attention

Back Up

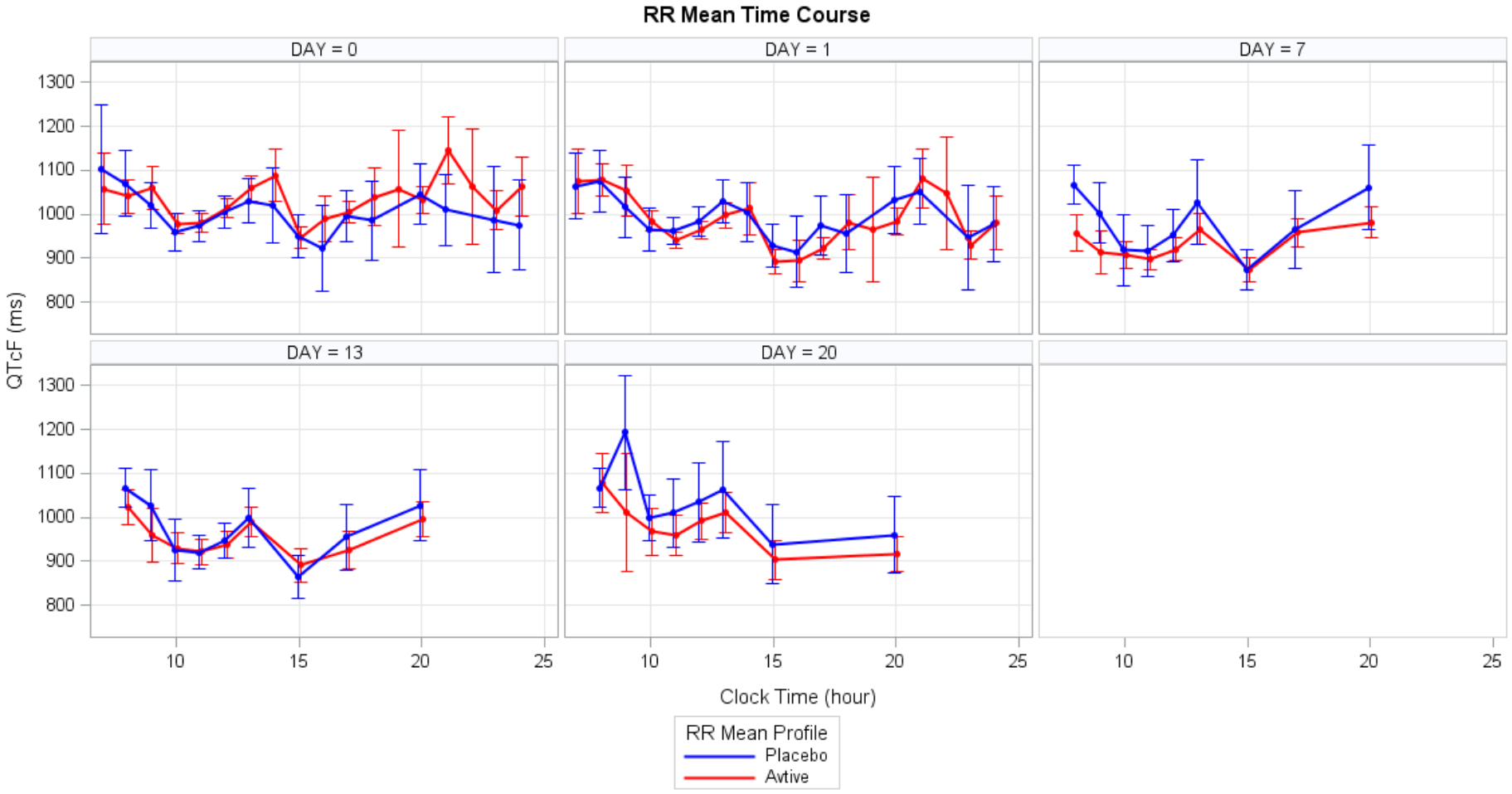
Circadian Rhythm



Placebo Effect

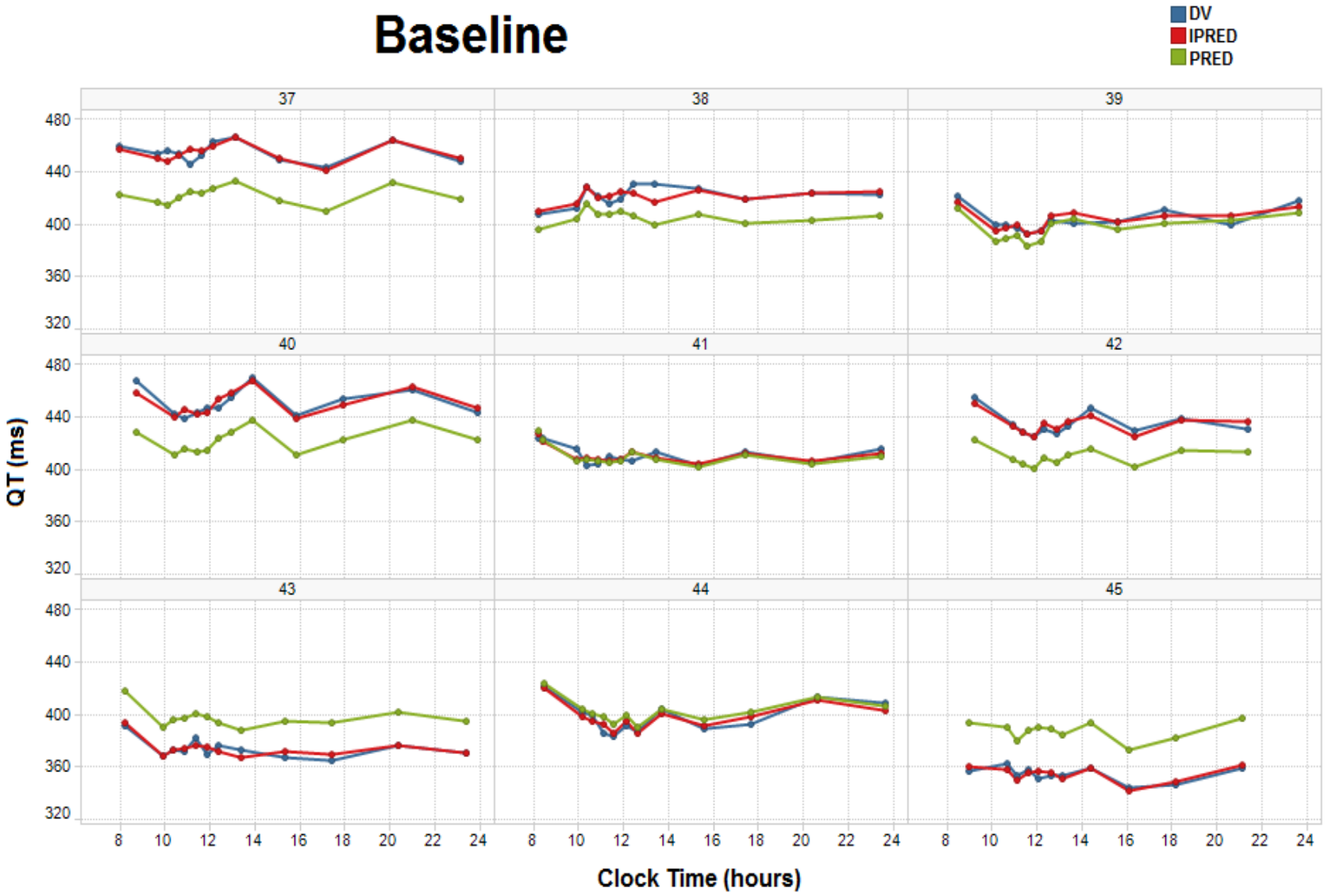


Drug Effect on RR

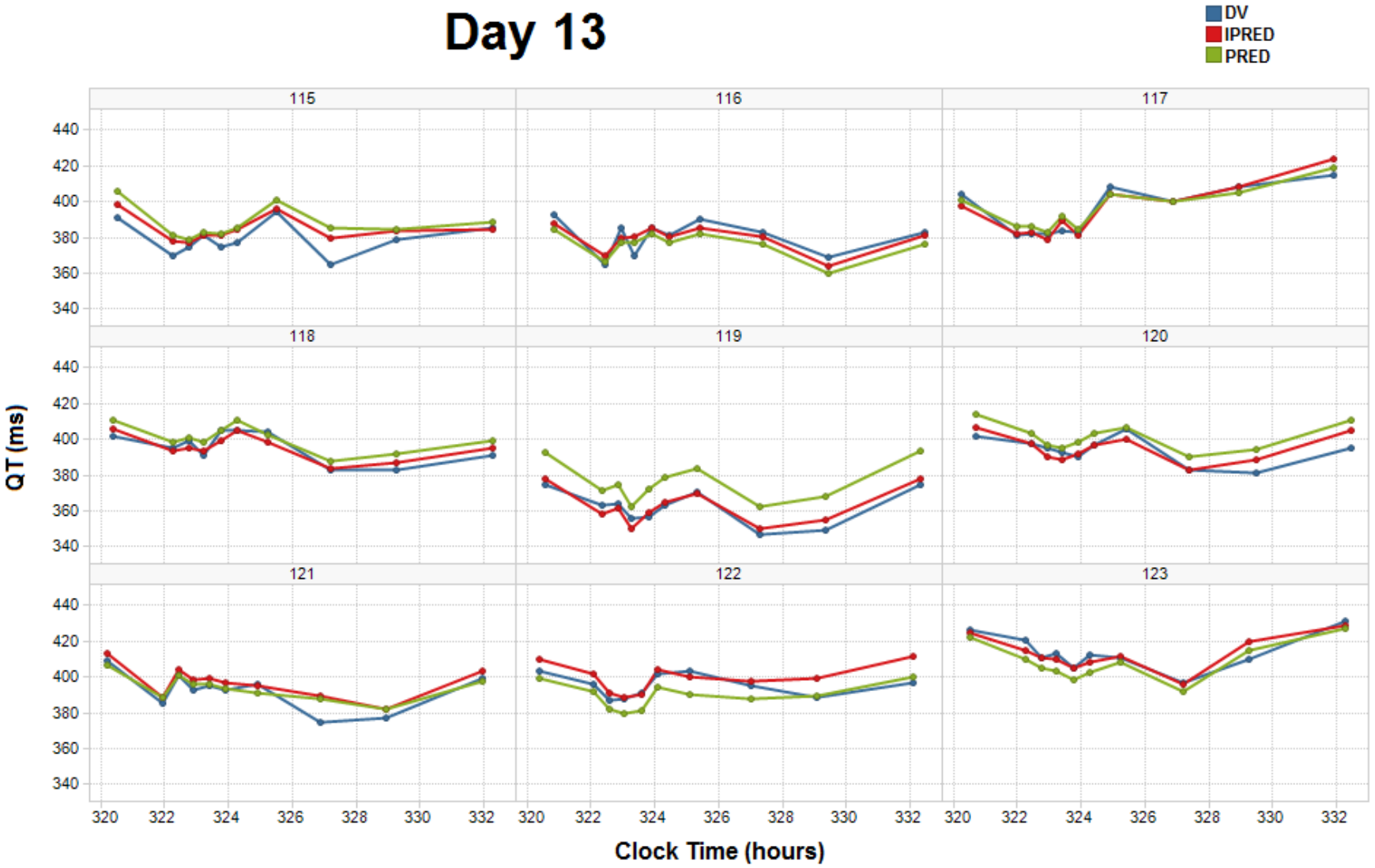


CI=mean+-1.96(std/sqrt(n))*

Individual Fits



Individual Fits



Doing now what patients need next