POPULATION PHARMACOKINETIC AND PHARMACODYNAMIC META ANALYSIS OF ZENVIA: MODELING OF QT PROLONGATION

J. Grenier[1] Ph.D., JR. Lavigne[1] M.Sc., LE. Pope[2] Ph.D.

[1] Clinical Pharmacology Department, Celerion, Montréal, Qc, Canada
[2] Avanir Pharmaceuticals, Aliso Viejo, CA, USA

celerion

INTRODUCTION

Zenvia is a combination of 2 approved drugs, Dextromethorphan (DM) and Quinidine (Q), and is being developed for the treatment of Pseudobulbar Affect (PBA). The limited systemic delivery to the central nervous system (CNS) of DM may be a limiting factor of its efficacy in the treatment of different neurological disorders. Q is used as an inhibitor of DM metabolism by CYP2D6 enzymes to increase its bioavailability. A dose combination of 30 mg DM with 30 mg Q b.i.d. was used during the early development of Zenvia. In order to improve the safety profile of the drug, the dose of Q was subsequently reduced to 10 mg b.i.d. The current dose formulations of Zenvia in development for the treatment of PBA are DM 20 mg/Q 10 mg, and DM 30 mg/Q 10 mg. This dose of Q in Zenvia is 1-3% of that used to treat arrhythmias.

OBJECTIVE

The objective of this study was to establish the relationship between the predicted plasma concentrations of Q, DM, and its metabolite Dextrorphan (DX) and the changes in QT intervals from baseline/placebo at 3 dose levels (including supratherapeutic).

DATA

The results of two thorough QT studies were combined. Both studies were randomized, placebo-controlled and positive-controlled (moxifloxacin). Three DM/Q dose levels were included in these studies: 30/10 mg (actual clinical dose), 30/30 mg (initial clinical dose) and 60/60 mg (supratherapeutic). Doses were given b.i.d. for 4 days. Plasma samples were collected on Day 4. A total of 82 subjects were included in the population PD analysis. Modeling was performed on all individual QT interval measurements and not on the averaged QT at each time point. A total of 7446 QT and corresponding RR intervals were used in the baseline/placebo analysis and a total of 11,382 QT and RR intervals were used in the QT change from baseline analysis. Baseline measurement were taken before all doses, including placebo. Because circadian rhythm was included in the model, clock time was used.

METHODOLOGY

Sequential modeling:
1. Q, DM and DX data from Study 1 were fitted using a maximum a posteriori Bayesian (MAPB) analysis with the previously developed population PK model (which included Study 2)
2. Q, DM and DX PK parameters were fixed for each individual and predicted concentrations were used for PK/PD modeling
3. Baseline and placebo QT intervals were fitted alone.
4. Baseline and placebo QT intervals PD parameters were individually fixed for the model discrimination of drug induced QT prolongation.

Covariates:
Age, gender, race, height, weight, body mass index - impact assessed graphically.
Sofware: ADAPT 5, Version 5.0.34, August 25, 2009, using ITS algorithm.[1]

RESULTS AND DISCUSSION

Baseline Model
The baseline correction methods were different between QT studies. Therefore, the analysis was performed directly on uncorrected for baseline QT intervals using all measurements. The first step was to model the observed baseline QT values.
The final model is described by the following equations.[2]
A truncated Fourier series was used to represent the circadian rhythm for QT, the QT measurement of individual i at time j :

$$QT_{baseline,ij} = QTc0_i \cdot RR_{ij}^{\alpha i} \cdot (1 + CIRC_i) \quad (1)$$

where $QTc0_i$ is an individual basal value of the corrected QT interval, RR_{ij} is the observed interval, α_i an individual exponent and $CIRC_i$ is the expression for the individual circadian rhythm.

$$CIRC_i = A_{1,i} \cos[2\pi(t - \phi_{1,i})/24]$$
$$+ A_{2,i} \cos[2\pi(t - \phi_{2,i})/12] + A_{3,i} \cos[2\pi(t - \phi_{3,i})/6] \quad (2)$$

where A and ϕ are the amplitudes and acrophases, respectively.

The CIRC function was also evaluated with 2 oscillators. The inter-occasion variability was first evaluated by fitting different QTc0i for each study day. The second approach allowed QTc0i to vary with its own truncated Fourier series, with one or two oscillators (equation 3). This second approach resulted in a better fit of the data.

$$QTc0_i = QTc0_i^0 \cdot \begin{pmatrix} 1 + A_{01,i} \cos(2\pi(t - \phi_{01,i})/24) \\ + A_{02,i} \cos(2\pi(t - \phi_{02,i})/12) \end{pmatrix} \quad (3)$$

With this model, placebo was not different from baseline. The final model was also evaluated with fixed exponent α, equivalent to the Bazett correction ($\alpha = 0.5$, QTcB) and the Fridericia correction ($\alpha = 0.33$, QTcF).

Figure 1: Comparison of the Corrections Factors for QT Measurements
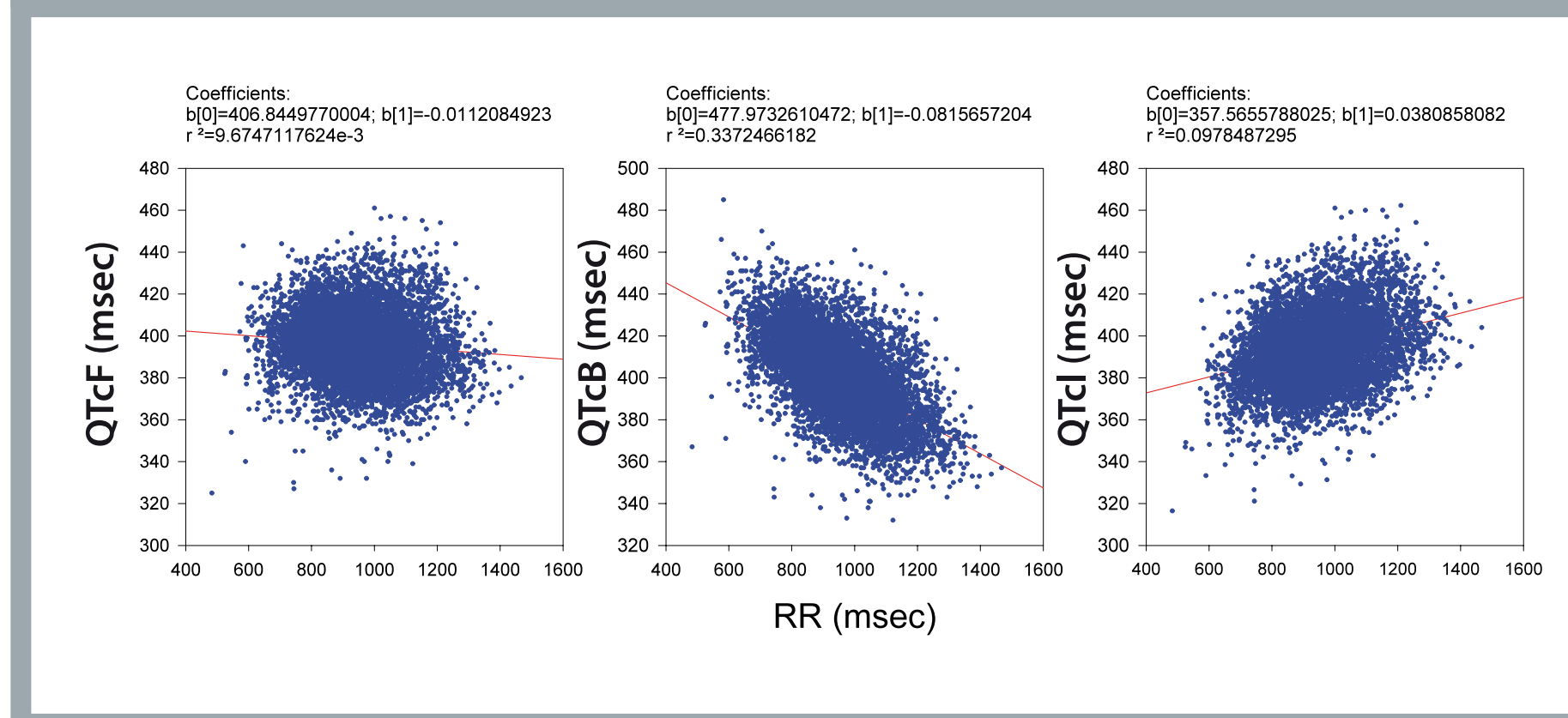
Although QTcF is the least biased correction, based on AIC values, individual corrections (QTcI) are more appropriate.

Drug-induced QT Changes from Baseline
Linear effect, Emax and sigmoidal models were each evaluated as direct and indirect effects for each analyte separately and then by combining of 2 or 3 PD models, using the best model for each analyte. The plasma Q concentrations were sufficient to explain the observed QT prolongation with a sigmoidal Emax model.

$$QT_{ij} = QT_{baseline,ij} + \frac{E\max_i \cdot C_{ij}^\gamma}{IC50_i^\gamma + C_{ij}^\gamma} \quad (4)$$

Where $Emax_i$ is the maximum QT prolongation for subject i, $IC50_i$ is the concentration of Q required to reach half the Emax value and γ is a Hill coefficient.

Figure 2: Typical QT vs Time profiles
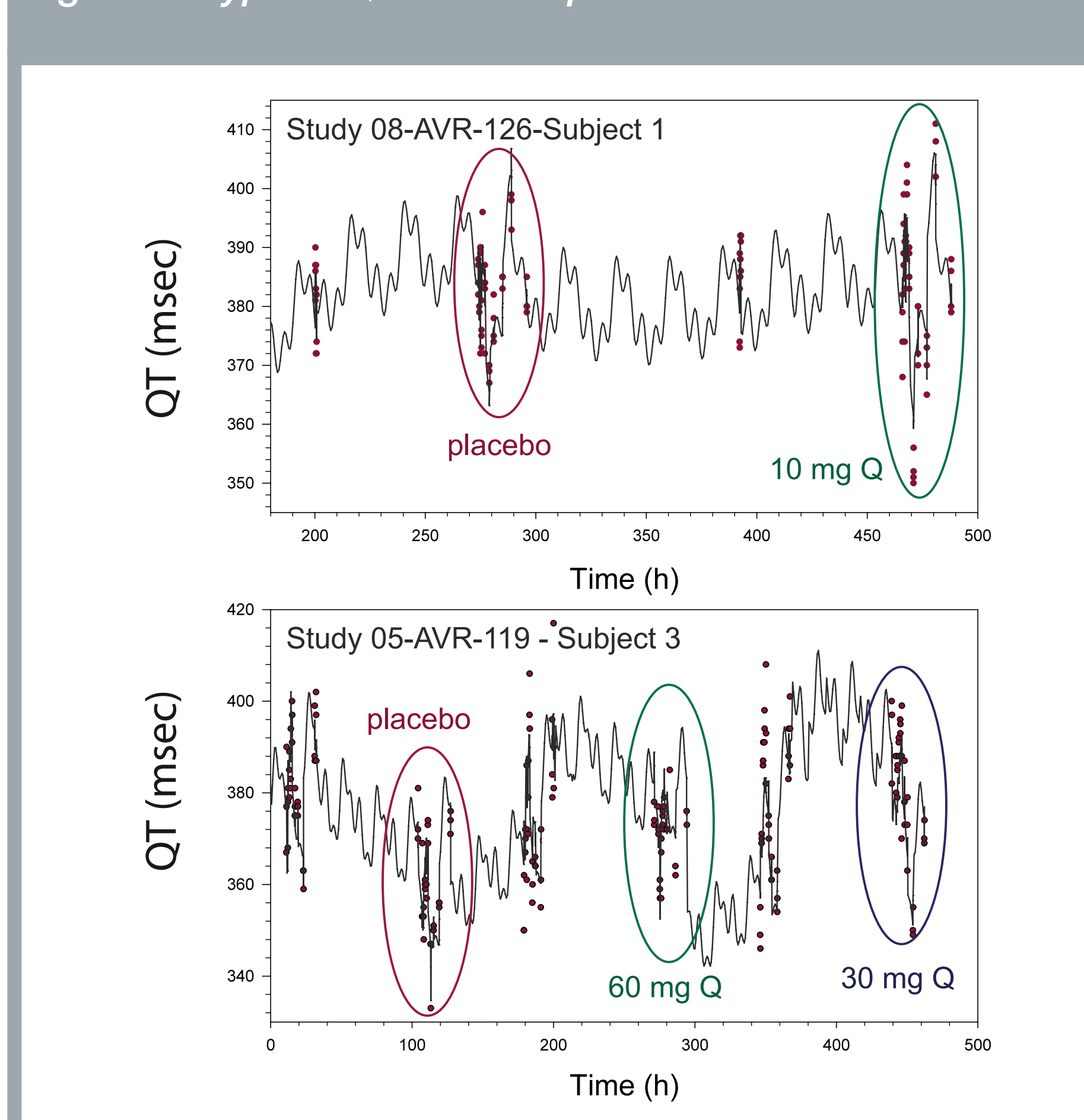
In addition, the best fit was obtained when refitting all parameters together. No covariate was deemed significantly correlated with any PD parameters.

Results from the best fit are presented in Table 1.

Table 1: Population PD Parameters for QT Intervals Following Population PK/PD Analysis

	Parameters	Mean	Inter-subject variability (%CV)**
Baseline	$QTc0^0$ (msec)	396	3.2
	A_1	0.0174	32.2
	ϕ_1 (h)	3.90	45.9
	A_2	0.00969	62.2
	ϕ_2 (h)	2.43	81.1
	A_3	0.00831	37.0
	ϕ_3 (h)	18.8	9.4
	α	0.224	23.2
Inter-occasion variability	A_{01}	0.0140	81.1
	ϕ_{01} (h)	195	56.5
	period1 (h)	434	27.1
	A_{02}	0.0184	47.0
	ϕ_{02} (h)	35.2	84.0
	period2 (h)	191	20.3
Change from baseline	Emax (msec)	17.0	50.3
	IC50 (ng/mL)	73.6	78.5
	γ	3.21	85.5
Intra-subject variability (%CV)*		1.97	

*Additive model best fitted the data; ** Parameters were normally distributed

Given the high variability in QT intervals, the characterization of the different sources of variability of the baseline is crucial to properly distinguish between measurement noise and true drug effect. The residual variability for the baseline modeling was 1.93%, indicating that most of the variations in QT intervals within an individual are well explained by the PD model.

The exponent α is treated as any other population parameter and previous works have shown that this is a very robust method for α determination.[3] The α values were similar following baseline and QT prolongation analyses, with mean values of 0.210 and 0.224 respectively, giving an indication that the α estimation is robust enough to be independent from the inclusion of QT data following drug administration.

Figure 3: Predicted QT Interval Changes over the Observed Quinidine Concentrations Following 10 mg Doses of Quinidine Sulfate BID for 7 Doses.
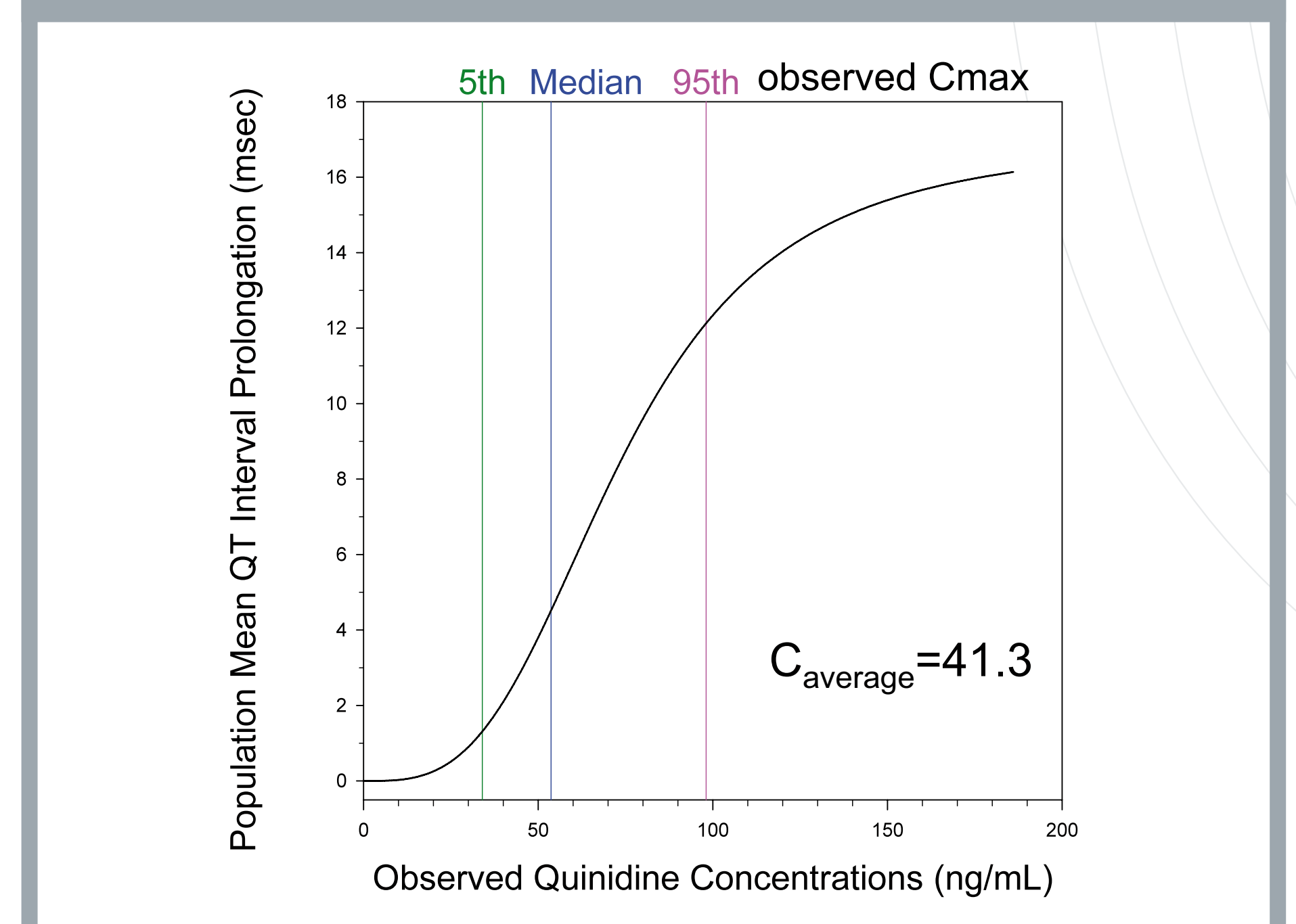
CONCLUSION

Overall, the baseline QT intervals and the drug-induced QT intervals change from baseline following Zenvia administration, described by a sigmoidal model, were well fitted with the population PK/PD model. Quinidine concentrations were sufficient to explain the observed drug-induced QT interval change from baseline following Zenvia administration. This type of model allows one to pool data from studies that originally used different baseline assessments. The method appears robust for baseline assessment. Baseline parameters were similar when baseline/placebo data were fitted alone (not shown) versus when all data were fitted altogether (Table 1).

REFERENCE

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3. Germani M et al., Nonparametric Modeling and Population Approach to the Individualized Heart Rate Correction of the QT interval. Downloaded from http://www.page-meeting.org/pdf_assets/4702-poster_page2008_Germani.pdf