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 Dextromethorphan (DX) and the changes in QT intervals from baseline/placebo at 3 dose levels (including supertherapeutic).

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 (supertherapeutic). 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 truncated Fourier series was used in the baseline/placebo analysis and a total of 3,182 QT and RR intervals were used in the QT change from baseline analysis. Baseline measurement was 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 of 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.

Pharmacodynamic models:
Linear effect, Emax and sigmoidal models were each evaluated as direct and indirect effects for each analyte separately and then by combining 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.

\[ \text{QTc}_i = \text{QTc}_0 + \frac{E_{\text{max}}}{C_{50i} + C_{	ext{Hill}}^2} \]  (4)

Where \( E_{\text{max}} \) is the maximum QT prolongation for subject i, \( C_{50i} \) is the concentration of Q required to reach half the Emax value and \( y \) is a Hill coefficient.

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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 was also evaluated with fixed exponent \( \alpha \), equivalent to the Bazett correction (\( \alpha = 0.5, \text{QTcB} \)) and the Fidcicria correction (\( \alpha = 0.33, \text{QTcF} \)).

\[ \text{QTcF}_i = \frac{\text{QTc}_i}{RTF} \]  (3)

With this model, placebo was not different from baseline.

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 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.

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).