

**Title: HIERARCHICAL BAYESIAN EXPOSURE-RESPONSE ANALYSIS AND STATISTICAL ASSESSMENT OF HEART RATE-CORRECTED QT INTERVAL (QTc) FOR TORCETRAPIB**

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**Objectives:** Torcetrapib is a cholesteryl ester transfer protein inhibitor previously in Phase 3 testing in combination with atorvastatin for treating dyslipidemias and altering the progression of atherosclerosis. The primary objective of this study was to demonstrate a lack of effect of torcetrapib/atorvastatin (T/A) fixed dose combinations on change in QTc, using Fridericia's correction method (QTcF), from time-matched baseline relative to placebo at the torcetrapib historical Tmax of 4 hours on Day 21 of dosing. Another objective was to characterize the exposure-response relationship between plasma concentrations of torcetrapib and the M1 metabolite (BTFMBA) and changes in QTc. The per protocol analysis results have been reported previously [1]. The objective of this communication is to evaluate a hierarchical Bayesian approach using Markov Chain Monte Carlo (MCMC) methods for analysis of QTc data.

**Methods:** This was a double-blind, randomized, multisite, parallel group, multidose thorough QT study in 389 healthy subjects. Subjects were given T/A 60/20 mg, 240/80 mg, or placebo (PBO) daily for 21 days. A fourth group received PBO for 20 days then open-label moxifloxacin (MOXI) 400 mg on Day 21 to confirm study sensitivity. Twelve lead electrocardiogram (ECG) measurements were made in triplicate, approximately 2 minutes apart and manually over read at a central lab. Plasma samples were analyzed for torcetrapib and BTFMBA using solid phase extraction followed by gas chromatography tandem mass spectrometry.

The per protocol analyses were an analysis of variance (ANOVA) using SAS PROC MIXED with treatment, sex, and site as fixed effects and an exposure-response (ER) model implemented using maximum likelihood (ML) methods in NONMEM V with fixed effects of baseline, PBO, and sex on intercept and separate slopes were estimated for both torcetrapib and BTFMBA concentrations. Separate simulation and nonparametric bootstrap procedures were employed to assess the predictive performance of the NONMEM model and to generate confidence intervals (CI) about the parameter estimates and the expected QTc response. The NONMEM model was translated into a Bayesian framework implemented in WinBUGS 1.4.3 [2] using noninformative priors for all parameters. Inferences about predictive performance, parameter estimates, and model predictions can all be obtained using samples from the joint posterior distribution which is generated during the estimation process.

**Results:** Mean (90% CI) Placebo-Corrected Change from Baseline QTcF Interval Estimates at 4 hours (T/A) and 2 hours (MOXI) on Day 21 from the Per Protocol (ANOVA and NONMEM) and WinBUGS analyses

Analysis Method	T/A		MOXI
	60/20 mg	240/80 mg	400 mg
ANOVA	-0.662 (-3.46, 2.13)	-0.750 (-3.25, 1.75)	6.14 (3.62, 8.65)
NONMEM ER Model	-0.406 (-1.05, 0.258)	-0.830 (-3.18, 1.58)	
WinBUGS ER Model	-0.663 (-1.57, 0.243)	-1.71 (-4.80, 1.40)	

**Conclusions:** Statistical analysis and exposure-response modeling support a lack of effect of T/A 60/20 mg and 240/80 mg on QTcF prolongation at the torcetrapib historical Tmax on Day 21. Employing hierarchical Bayesian methods affords some process efficiencies over maximum likelihood approaches for model evaluation and making inferences based upon the model results.

**References:**

[1] Riley SP, LaBadie R, Terra SG, Kolluri S, Thuren T, Shear C, Russell T, Benincosa LJ, Gibbs M. Mixed Effects Exposure-Response Analysis and Statistical Assessment of Heart Rate-Corrected QT Interval (QTc) for Torcetrapib. *Clin Pharmacol Ther* 81 (Suppl1): Abstract PII-74, S73, 2007.

[2] Lunn, D.J., Thomas, A., Best, N., and Spiegelhalter, D. (2000) WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*, **10**:325--337.