Evaluation of Power of Linear Mixed Effect (LME) and Linear Median Quantile Mixed (LMQM) Modeling to Predict Through-QT (TQT) Study Outcomes Using a Single Dose Arm (SDA) Data of Phase I Studies

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Objectives: To evaluate the power of LME and LMQM in predicting TQT study outcomes using the typical sample size of a SDA data of Phase I studies.

Methods: Simulation studies were conducted for 2 scenarios: one is for a moxifloxician-like positive TQT study with the maximum upper bound of 90% confidence of baseline- and placebo- subtracted QTcF across sampling times (MΔΔQTcF >10 msec, the other is for a negative TQT study with MΔΔQTcF < 5 msec. QTcF and concentration (CONC) data of 60 subjects from a cross-over TQT study of AZD5672 with positive control of 400 mg moxifloxician (MΔΔQTcF =12 msec) and negative QTcF prolongation of AZD5672 150 mg (MΔΔQTcF =2 msec) were used for simulations. 1000 SDA data sets of QTcF and CONC data were simulated for each scenario. For each simulated data set, 9 subjects (3 for placebo and 6 for active treatment) were sampled without replacement from 60 subjects to mimic the typical design of the SDA of Phase I studies. R packages LME4 and LQMM were used to model the relationship between CONC and ΔQTcF for each simulated data set. QTcF prolongation was calculated as the 95th percentile of 3000 bootstrapping replicates for the mean QTcF prolongation at the geometric mean CONC for each replicate. The power was calculated as % 1000 simulated SDA data sets that concluded the correct positive or negative TQT study outcomes.

Results: The estimated power to predict moxifloxician-like positive TQT study are 94.4 % and 98% for LME and LMQM, respectively, while the estimated power to predict the negative TQT study are 96 % and 97.5% for LME and LMQM, respectively.

Conclusions: For a compound with moxifloxician-like positive or little ΔQTcF prolongation, both LME and LMQM provide high power to predict correct TQT study outcomes using typical SDA data. LMQM provides further improvement to the power.