Assessment of Azeliragon QTc Liability Through Integrated, Model-Based Concentration-QTc Analysis

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Introduction

Azeliragon is an orally bioavailable inhibitor of the receptor for advanced glycation endproducts (RAGE). In transgenic mouse models, azeliragon reduces neuroinflammation, Aβ transport into the brain and Aβ deposition, and improves both regional cerebral blood flow and cognitive performance. Phase 2 results demonstrated that subjects with mild-to-moderate Alzheimer's disease (AD) (MMSE14-26) treated with azeliragon 5 mg/day had a decreased decline in ADAS-cog11 at 18 months compared to placebo (Δ =3.1, p=0.008) and the mild AD subgroup (MMSE 21-26) had both decreased ADAS-cog decline compared to placebo (Δ = 4.0, p=0.02) and decreased decline in CDR-sb (Δ=1.0, p=0.02). In the Phase 2 study, azeliragon 5 mg/day delayed the time to cognitive deterioration (defined as a 7-point worsening in ADAS-cog) relative to placebo in patients with mild AD with a hazard ratio of 0.5 (logrank p=0.02).

Azeliragon, is currently being evaluated in a pivotal Phase 3 study for efficacy and safety in patients with mild AD.

Clinical studies conducted to date with thorough collection of 12-lead ECGs throughout treatment have not shown a signal for QT prolongation due to azeliragon.

A concentration-driven, model-based analysis of the relationship between azeliragon plasma concentration and change in QTc was conducted as supported by ICH E14 Q&A updated, December 2015.

Objective

The objectives of this concentration – QT analysis were:

- To evaluate whether there is a relationship between plasma azeliragon concentrations and its major metabolites and changes in the RR interval or QT interval.
- To predict drug-related changes in QT at therapeutic (5 mg QD) and supra-therapeutic doses (20 mg QD)

Methods

- Simultaneous (within ± 30 minutes) plasma concentration-time and 12-lead ECG measurements were pooled from 5 studies in healthy volunteers, 2 studies in patients with mild-to-moderate AD, and one study in patients with Type 2 diabetes and persistent albuminuria.
  - 711 subjects from 8 studies contributing 6236 paired observations from single doses of 5 to 65 mg and repeat doses of 5 to 60 mg QD.

Methods

Population	Number of Unique Subjects	Number of Paired Observations	Azeliragon Dosing
Healthy Volunteers	131	2048	Placebo Single doses (5-65 mg) Repeat doses (5-20 mg)
AD patients	470	3462	Placebo Repeat doses (5-20 mg)
Type 2 Diabetes	110	726	Placebo Repeat doses (20 mg)

Population Pharmacokinetic Methods

- Nonlinear mixed effects modelling (NONMEM® version 7.3, ICON Development Solutions, Ellicott City, MD) was used to describe the azeliragon concentration-related changes in QT interval, after correcting for heart rate effects using Frederica's criteria (QTcF) and gender-related changes in baseline QTcF.
  - Age, triplicate vs single ECG readings, and manual vs computerized ECG readings on QT interval were not statistically significant covariates and were thus not included in the final model.
  - Diurnal variation (<1 msec) in QTcF was not clinically evident.
  - No additional effect of metabolites (M1, M2, M3) on QT was identified using a subset of the data from drug metabolism study after fixing parameters for the parent compound.
  - Residual variability was addressed using an additive error model with different terms for healthy volunteers versus patients.
  - Final model was evaluated using goodness-of-fit plots, a nonparametric bootstrap procedure, and visual predictive check (VPC)
- Azeliragon-related changes in QTcF predicted using two methods:
  1. Simulation Approach: (accounted for inter-individual variability and parameter uncertainty), 1000 simulations were conducted within ModelRisk by:
     a) Randomly selecting an observed Cmax value following 5mg QD at steady state (therapeutic dose) and following 60 mg QD on Day 6 or 20 mg QD at steady state (supratherapeutic doses) for each simulation
     b) Randomly selecting a concentration-related slope and its inter-individual variability (IIV) from the nonparametric bootstrap for each simulation
     c) Multiplying Cmax by the concentration-related slope and IIV parameters for each simulation
     d) Summarizing the median and 90% confidence interval for the drug-related QT effects at therapeutic and supratherapeutic doses across all simulations
  2. IQ-CSRC Approach: suggested by the International Consortium for Innovation and Quality in Pharmaceutical Development and the Cardiac Safety Research Consortium (IQ-CSRC).
     - Two-sided 90% confidence intervals of the estimate calculated using a bias-corrected nonparametric bootstrap. Geometric mean Cmax multiplied by the upper 90% confidence interval of the concentration-related slope.

Results

Fig 1. Goodness-of-Fit Plots Including Observed (DV) vs Population Prediction (PRED), DV vs Individual Predicted (IPRED), Conditional Weighted Residuals (CWRES) vs IPRED, Histogram of CWRES, CWRES vs Time, and CWRES vs IPRED for the Final C-QT Model of Azeliragon

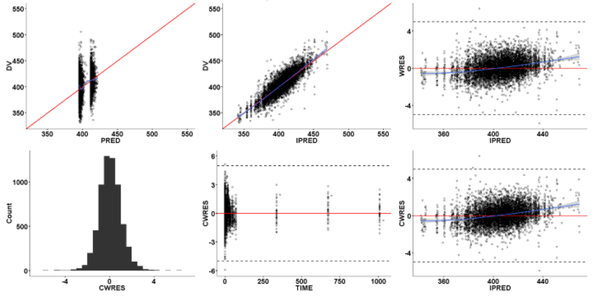
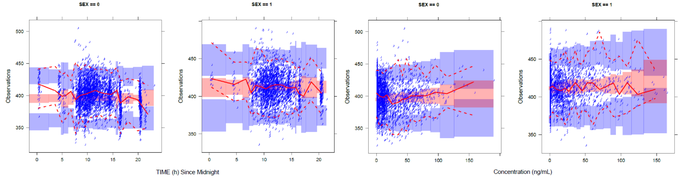


Fig 2. Visual Predictive Check (VPC) of Observations (QTcF, msec) Plotted Against Time of Day (hour) [graphs on left] and Plasma Concentrations (ng/mL) [graphs on right] Separated by Sex for the Final C-QT Model for Azeliragon



- ❑ For both VPCs, the 97.5th, 50th and 2.5th percentiles (shown as red lines) fall within 95% confidence interval (shown in shades) of the 1000 simulated data.
- ❑ Based on the VPC and bootstrap analysis the final model is appropriate for simulations

Final Parameter Model:

Baseline QTcF = TVP_{QTcFki}*(1+SLP*SEX) + η_i

Where TVP_{QTcFki} is typical value of baseline for the ith individual; sex=0 for males and 1 for females and SLP is the slope describing additive effect of female gender on baseline QTcF with interindividual variability (IIV) on baseline QTcF as an additive error model where η_i represent IIV with a mean of 0 and SD of sqrt(η_i)

QTcF = Baseline QTcF +CONC*(CSLP + η_i) + eps

Where CONC is the plasma concentration of azeliragon; CSLP is the concentration-related slope. IIV added to CSLP as additive error model; eps represents residual variability as an additive error model with a mean of 0 and an SD =sqrt (eps) with different values of eps for healthy volunteers and patients.

Parameter Estimates from Final C-QT Model

Parameter	Estimate (%RSE)	Bootstrap Estimates Median (90% CI)
Baseline QTcF in Males (msec)	395 (0.44%)	395 (393-397)
Additive Sex Effect on Baseline QTcF for Females (%)	0.0420 (11.4%)	0.0422 (0.0361 – 0.0484)
Resulting Baseline QTcF in females (msec)	412	412 (410-415)
IIV on Baseline (± msec)	±16.4 (6.65%)	±16.4 (15.5 – 17.4)
Residual Error in Healthy Volunteers (± msec)	±9.83 (6.72%)	±9.80 (9.29 – 10.3)
Residual Error in Patients (± msec)	±12.6 (5.07%)	±12.6 (12.0 – 13.1)
Concentration Effect on QTcF		
Concentration-related slope on QT (msec/ng/mL)	0.0590 (19.2%)	0.0583 (0.0408 – 0.0766)
IIV on Concentration-related slope	±0.0881 (136%)	±0.0929 (0.0599 – 0.133)

IIV: inter-individual variability; RSE: relative standard error; msec: CI: confidence interval

Results from Simulations: Predicted Cmax and Drug-Related Change in QTcF. Presented as median and 90% confidence interval

Dose	Predicted Cmax (ng/mL)	Predicted Drug-Related Change in QTcF (msec)
5 mg QD at steady state	11.0 (5.24 – 23.7)	0.733 (0.320 – 1.66)
20 mg QD at steady state or 60 mg QD for 6 days	66.0 (26.5 – 122.9)	4.32 (1.70 – 8.74)

- ❑ Using bias-corrected confidence intervals, the upper 90% confidence intervals for therapeutic and supra-therapeutics dose are 0.88 msec and 5.01 msec, respectively.

Conclusions

- There is a small positive relationship between azeliragon concentration and QTcF with a non-clinically meaningful slope close to zero.
- The upper bound of the 90% CI did not reach 10 msec, demonstrating that a drug-related effect on QTcF could be ruled out at therapeutic and supra-therapeutic doses.
- These results indicate that no deleterious effect of azeliragon is expected on QT at therapeutic and supra-therapeutic doses.