Population Pharmacokinetic Modeling of Riluzole After Administration of a Next Generation Prodrug Troriluzole

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Background: Troriluzole and Neurological Disorders

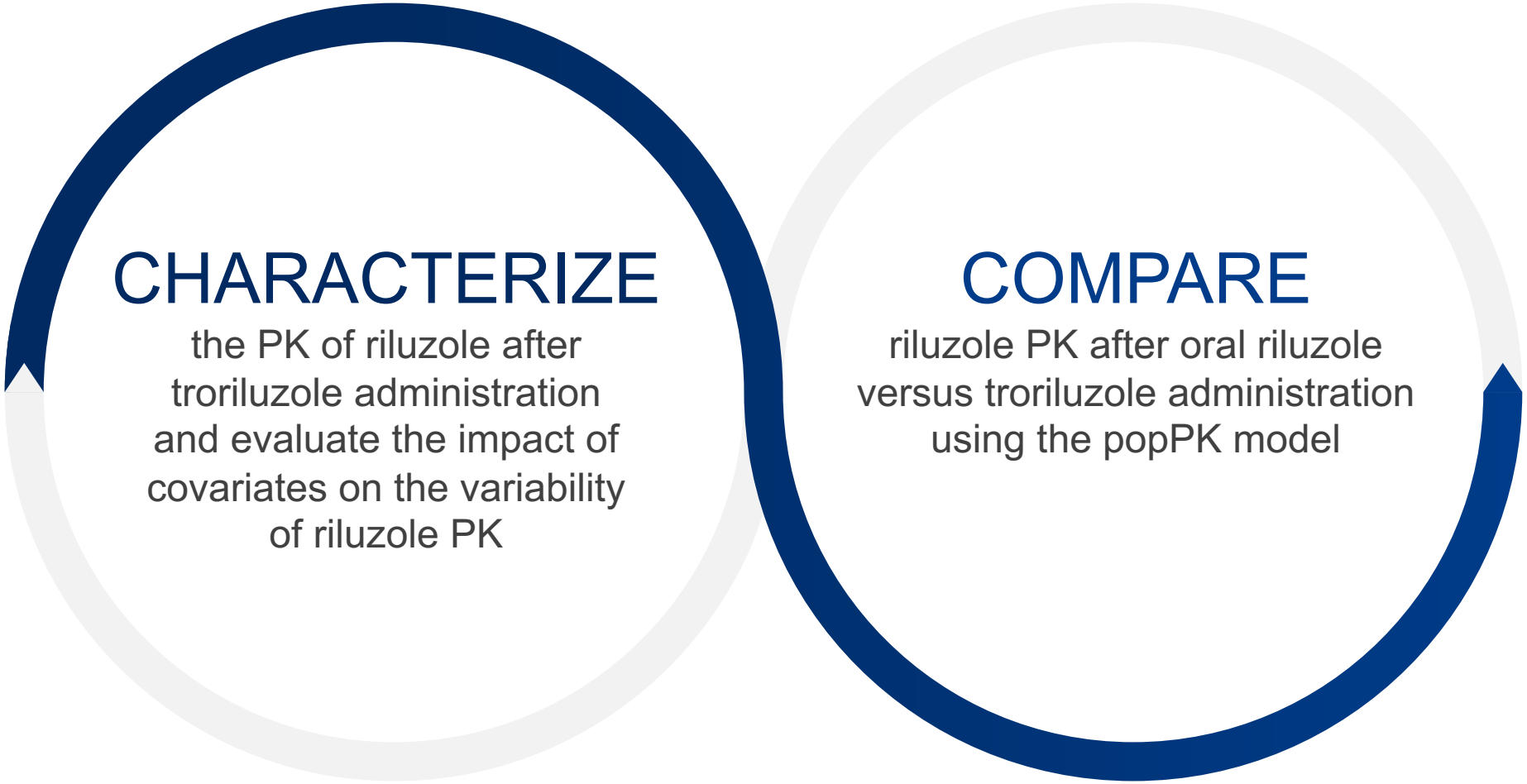
- Troriluzole, a third-generation tripeptide prodrug, was designed to improve the bioavailability, delivery and safety of the glutamate modulator riluzole
  - Riluzole is approved by the FDA for the treatment of amyotrophic lateral sclerosis (ALS)

- Riluzole use has been limited due to factors including:
  - High pharmacokinetic (PK) variability
  - Elevated liver function tests
  - Negative food effect
  - Relatively low bioavailability, and
  - Requirement for twice-daily dosing

- Troriluzole, which metabolizes in the body into the active metabolite riluzole, was developed to improve the PK and therefore the treatment potential, efficacy and safety of riluzole for use in neurological and neuropsychiatric disorders

Background: Troriluzole Population Pharmacokinetic Model

A troriluzole population PK (popPK) model was developed with the following objectives:



Methods

- The analysis included:
  - Eight Phase 1 studies in healthy subjects receiving troriluzole
    - One of the Phase 1 studies included subjects with moderate hepatic impairment
  - Five Phase 2 or 3 studies in patients receiving troriluzole
  - One Phase 1 study in healthy subjects receiving oral riluzole

- Quantifiable plasma concentrations of riluzole were available for:
  - 169 healthy subjects receiving troriluzole
  - 810 patients receiving troriluzole
  - 134 healthy subjects receiving riluzole

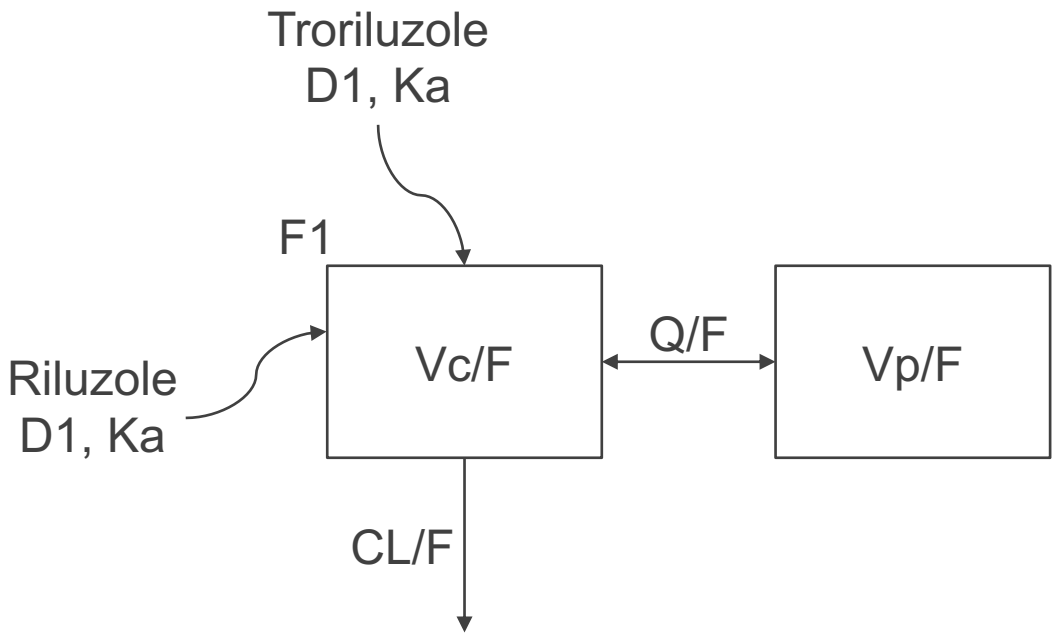
- Data analysis, popPK model evaluation, and postprocessing were conducted in NONMEM Version 7.4.4 and R Version 4.1.3

- The popPK model was used to simulate steady-state PK profiles of riluzole following repeated daily (QD) doses of troriluzole or molar equivalent QD doses of oral riluzole

Results

- The PK of riluzole after oral riluzole or troriluzole administration is described by a two-compartment model with separate zero-order followed by first-order absorption for each drug, linked together by relative bioavailability (F)
- Goodness of fit plots showed acceptable model fit for riluzole after either oral riluzole or troriluzole administration (next slide)
- In Phase 1 and moderate HI subjects with traditional sampling, riluzole had ≥50% lower inter-individual variability (IIV) on the absorption parameters Ka and F1 following troriluzole administration compared to riluzole administration

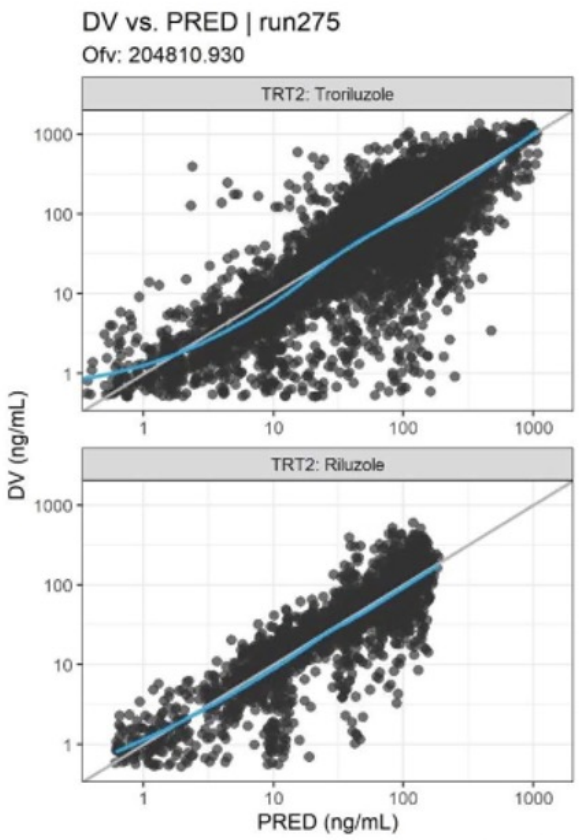
Schematic of PopPK Model After Riluzole or Troriluzole Administration

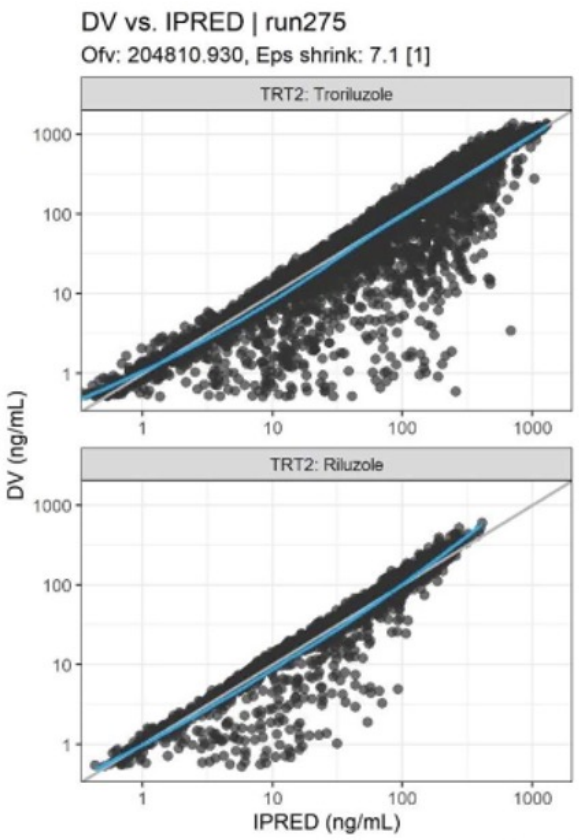


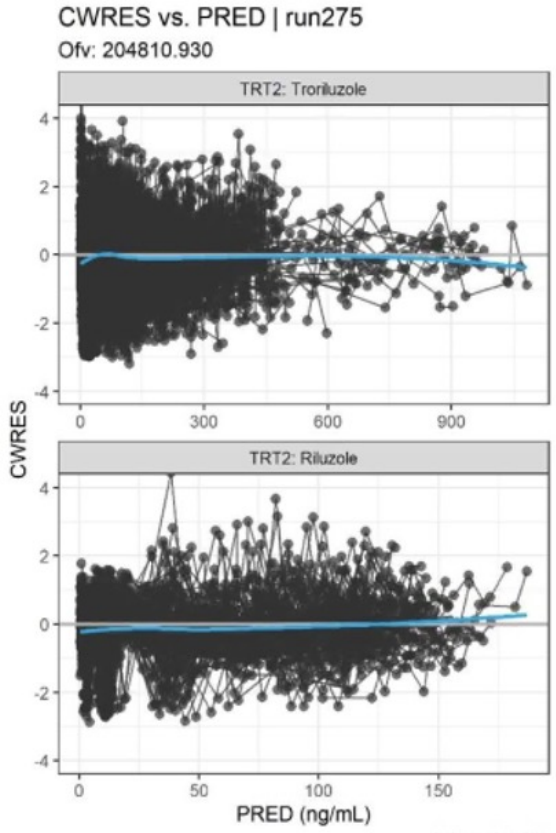
- Allometric weight centered on 70 kg was incorporated on CL/F and V/F terms with exponents of 0.75 and 1, respectively
- Statistically significant covariates in the final model included food or evening dosing on Ka, concomitant fluvoxamine, sex and age on CL/F

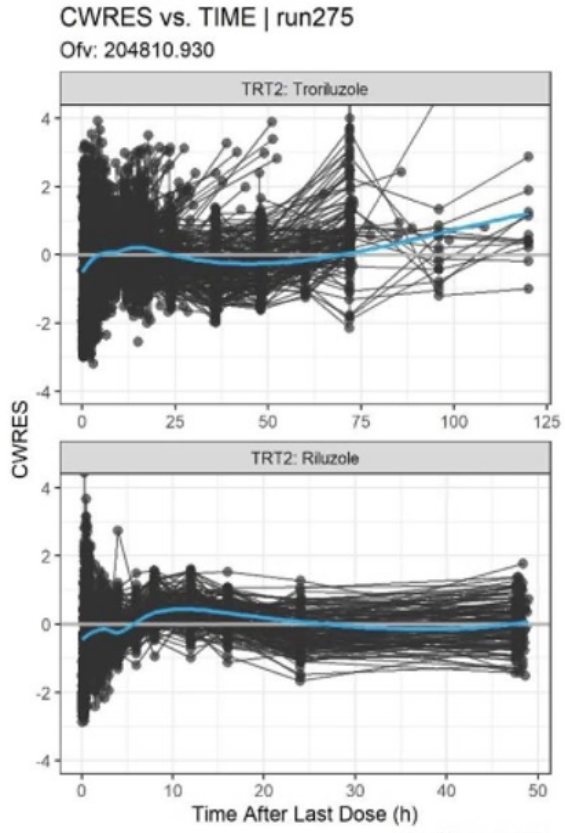
Results

Basic Goodness of Fit Plots for the Final PopPK Model









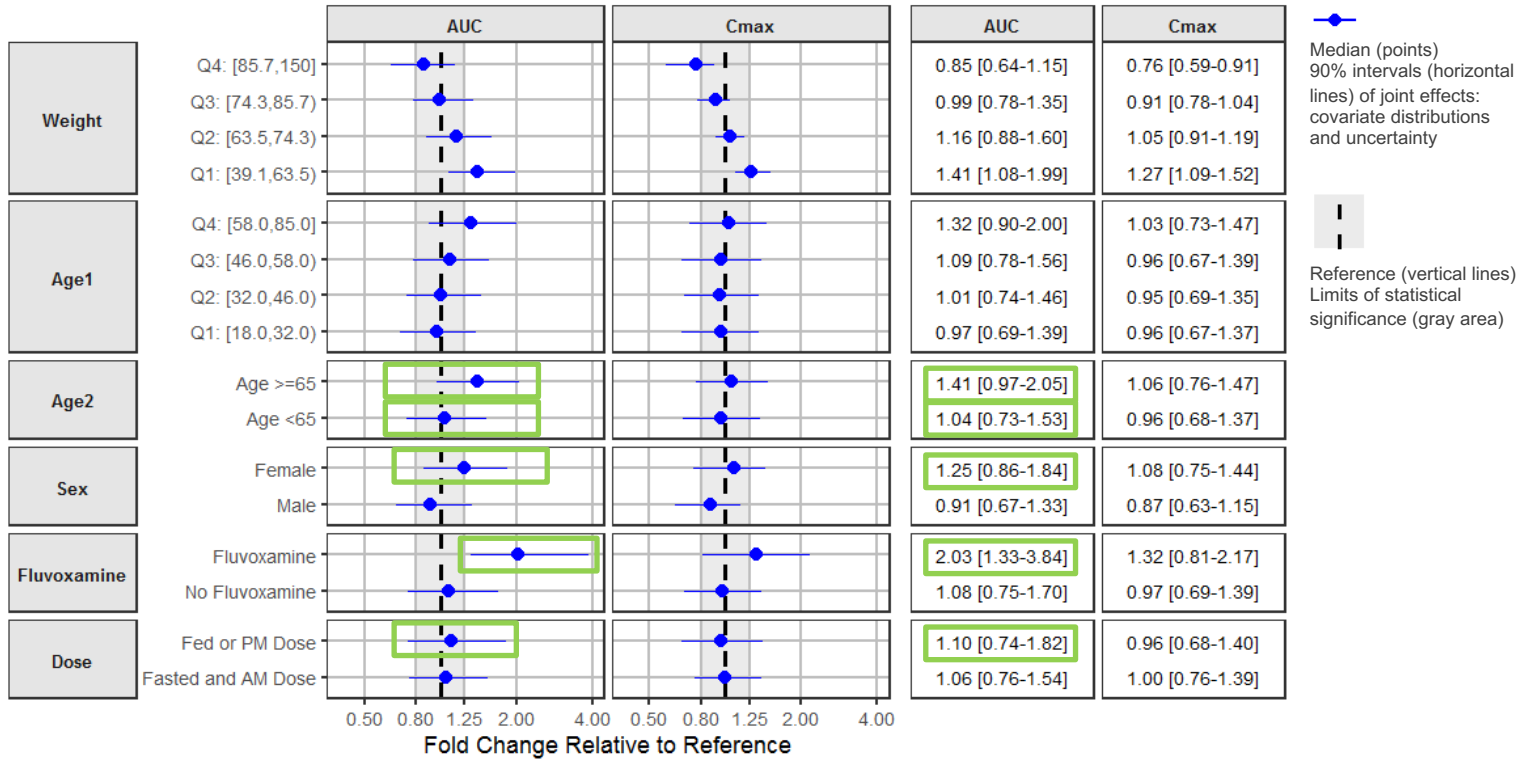
Results: Covariate Analysis

- Dosing of troriluzole with food or in the evening was associated with a 30.8% decrease (slower) Ka although the change in AUC and C_{max} was ~10% and ~4%, respectively

- Sex and age were statistically significant, but not considered clinically relevant
  - There were modest decreases in CL/F (~22.3% for female sex and ~13.9% for 65 versus 45 years of age)

- Concomitant fluvoxamine use (a strong CYP1A2 inhibitor) was associated with 55.6% decrease in CL/F and an average increase of 2.0-fold in AUC compared to the reference

Predicted Fold Change in Steady-State Riluzole AUC or C_{max} Relative to Reference

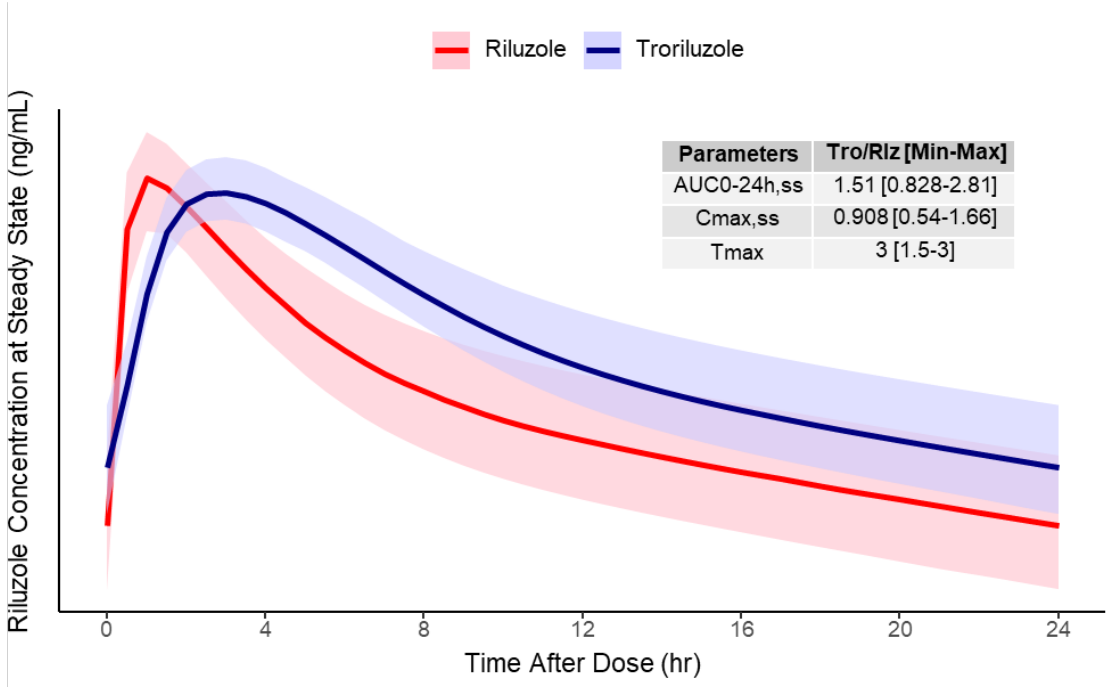


Data from 250 simulated trials of n=1080 subjects/trial. The reference (vertical dashed line and grey area) represents a 46-years old male subject, no fluvoxamine, dosed in the morning and in fasted state. Q = quartile of continuous covariates

Results: Model Predictions for Equimolar Troriluzole and Riluzole Doses

- Predicted exposure to riluzole during dosing interval ($AUC_{0\text{-}24h}$) was ~50% higher with troriluzole administration than with oral riluzole
- Despite higher bioavailability, the predicted riluzole $C_{max,ss}$ was similar after troriluzole and riluzole
- Predicted riluzole T_{max} after troriluzole occurred later than T_{max} after riluzole administration
- Higher concentrations of riluzole administered as troriluzole at 24 hours along with the delayed appearance of riluzole represents optimization for QD dosing

Log-linear Plot of Model-predicted Steady State Riluzole Plasma Concentration-time Profile at Once Daily Doses



Blue solid line and shaded area represent the median riluzole plasma steady state concentration and 90% prediction interval after troriluzole QD administration, respectively. Red solid line and shaded area represent the median riluzole plasma steady state concentration and 90% prediction interval after administration of equimolar oral riluzole QD doses. Inset table shows the ratios of steady-state riluzole $AUC_{0\text{-}24h}$, C_{max}, and T_{max} from troriluzole once daily relative to simulated equimolar oral riluzole once daily doses summarized as median and range. N=175

Conclusions

- Troriluzole, a novel, optimized, prodrug was rationally designed to overcome the shortcomings of oral riluzole
- The cross-study popPK analysis quantifies the distinct PK advantages of troriluzole over riluzole and support once-daily dosing without regard to food
  - Advantages include higher bioavailability and lower peak to trough ratio, longer absorption duration, lower PK variability versus riluzole and no clinically significant food effect
- The analysis supports the continued clinical development of troriluzole in neurological and neuropsychiatric conditions involving abnormal glutamate levels

Thank you!

Backup Slide(s)

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Fixed Effect Parameters

	Estimate (%RSE)
Riluzole Absorption Parameters	
Ka (h^{-1})	3.15 (6.7%)
D1, duration of zero-order release (h)	0.512 (3.3%)
Troriluzole Absorption Parameters	
Ka (h^{-1})	0.8 (12.3%)
Ka, Fractional effect of food or evening dose	-0.308 (26.4%)
D1, duration of zero-order release (h)	1.4 (3.9%)
F1, Fractional effect of troriluzole[a]	0.538 (13.7%)
Systemic PK Parameters	
CL/F (L/h)	67.9 (3.5%)
CL/F, Fractional effect of male sex	0.223 (12.8%)
CL/F, Fractional effect of fluvoxamine	-0.556 (5.8%)
CL/F, Fractional effect of age	-0.00728 (12.7%)
Vc/F (L)	285 (4.6%)
Vp/F (L)	457 (3.5%)
Q/F (L/h)	49.2 (4.8%)

a. Fractional effect of troriluzole to riluzole administration, transformed from the NONMEM estimate of -0.24 to account for molecular weight difference in dose (dose of troriluzole is expressed as troriluzole chloride monohydrate salt [molecular weight 473.85 g/mol] while dose of riluzole is expressed as riluzole base [molecular weight 234.2 g/mol]).

Random Effects and Residual Variability

	Estimate (%RSE) [Shrinkage]
Interindividual Variability	
IIV on CL/F of Phase 1 subjects (CV%)	19.2 (6.6%) [48.6%]
IIV on F1 of Phase 1 subjects on riluzole (CV%)	34.8 (6.7%) [64.5%]
IIV on Ka of Phase 1 subjects on riluzole (CV%)	88.0 (8.2%) [67.4%]
IIV on D1 of Phase 1 subjects on riluzole	44.6 (7.7%) [73.3%]
IIV on F1 of Phase 1 subjects on troriluzole (CV%)	17.9 (17.1%) [71.2%]
IIV on Ka of Phase 1 subjects on troriluzole (CV%)	34.6 (15.4%) [75.6%]
IIV on CL/F of patients (CV%)	64.6 (11.8%) [25.7%]
IOV on Ka of Phase 1 subjects on troriluzole	47.9 (9.5%)
IOV on D1 of Phase 1 subjects on troriluzole	62.7 (4.2%)
IOV on F1 of Phase 1 subjects on troriluzole	17.8 (13.3%)
Residual Variability	
Proportional error on Riluzole (%)	30.1 (2.0%)
Proportional error on Phase 1 subjects taking troriluzole (%)	31.3 (2.0%)
Proportional error on patients taking troriluzole (%)	52.2 (2.9%)

IIV = inter-occasion variability; IOV = inter-occasion variability; RSE = relative standard error