The effect of rufinamide concentration on the QT interval in healthy subjects treated during 18 days with multiple ascending doses: a population PKPD analysis

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Introduction

Rufinamide is a new chemical entity that modulates the frequency of sodium-dependent neuronal action potentials. Data from pre-clinical studies have demonstrated that rufinamide has activity in a broad range of animal models of epilepsy. Efficacy of rufinamide has been confirmed in epilepsy including Lennox-Gastaut syndrome in clinical studies in adults and children.

Objectives

- To evaluate the cardiovascular safety, the tolerability and the pharmacokinetics of rufinamide.
- To determine the maximum tolerated dose in healthy subjects.

Methods

Study design:

- Randomised double-blind, placebo controlled, multiple rising doses.
- 20 healthy male and female subjects, 5 received placebo, 15 received rufinamide.
- Repeated administration of rufinamide b.i.d. over 18 days with food.
- Doses: 800/ 1600/ 2400/ 3200/ 4800/ 7200 mg per day, during 3 days for each dose level.

Sampling strategy:

- PK assessments: pre-dose was taken at the start of the study, 9 PK samples were collected on the last day of dosing at each dose level: a total of 55 samples per subject.
- ECG assessments: screening, 4 recording before treatment and up 67 recordings per subject during the treatment.

Modelling:

- NONMEM (version level 1.1 double precision with Fortran digital compiler). First order conditional estimation method was used.
- Population modelling of rufinamide concentration and of ECG data was sequential.

Pharmacokinetic analysis

Structural model:

- A one compartment model with first-order absorption and first-order elimination.
- The effect of the dose/kg (DDKG) on the bioavailability was estimated using an E_{max} model.

Covariate model:

- Effects of demographic factors were tested on the PK parameters.
- Significant covariate was BSA on the CL and on V.

Random effects model:

- Between-subject variability was estimated on the parameters: CL, Ka and D50 using an exponential model.
- Proportional residual error model was preferred.

The parameters estimates, standard error of the estimate (SEE) and the %CV for the between-subject variability are summarized in Table 1. Rufinamide concentration data (predicted and observed) are presented in Figure 1.

Parameters	Estimate	SEE	
Fixed Effects			
CL= θ_1+(BSA/1.79) $^{\theta_6}$			
θ_1 intercept (L/h)	2.82	0.292	
θ_6 Effect of BSA on CL	5.9	0.751	
V= θ_2+θ_7 (BSA - 1.79)			
θ_2 intercept (L)	32.2	3.25	
θ_7 Effect of BSA on V	25.6	6.54	
k_a = k_a + θ_3			
θ_3 (h^{-1})	0.0791	0.0404	
F1=1+(θ_4*DDKG/(θ_5+DDKG))			
θ_4 Emax effect of DOSE	-1.18	0.159	
θ_5 DOSE for 50% of the effect (mg/kg)	101	28.1	
Random effects			Variability (% CV)
Between-subject variance / Exponential model			
ω^2 of CL	0.0344	0.0158	18.5
ω^2 of ka	0.0385	0.0219	19.6
ω^2 of D50	0.0607	0.0304	24.6
Proportional residual error			
σ^2	0.0117	0.00152	10.8

Table 1: Rufinamide PK parameters, final model, total daily dose per kg body weight ((BSA: body surface area (m^2)), DDKG: daily dose per kg (mg/kg), k_a = CL/V (h^{-1}))

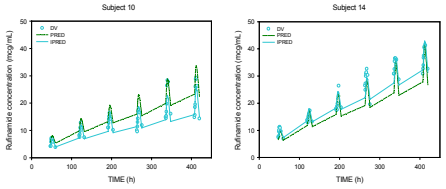

Fig. 1: Predicted (PRED and IPRED) and observed (DV) rufinamide concentration-time data, examples of 2 subjects

Pharmacodynamic analysis

Structural model:

- The analysis of QT was preceded by the analysis of drug effect on heart rate (HR).

Heart rate

- The effect of placebo/time in the study is described by an E_{max} relationship.
- A simple model for heart rate was developed, including a baseline heart rate, an increase of heart rate during the study time and an increase proportional to rufinamide concentrations.

$$HR = \theta_1 + \left(\frac{\theta_2 \cdot TIME}{\theta_4 + TIME}\right) + \theta_3 \cdot CONC + \eta_1$$

- Rufinamide effect was proportional to its concentration, with an increase of 0.182 bpm per 1 μg/mL.
- Rufinamide effect on heart rate confirmed that the best correction for the QT interval study is subject specific (QTc_{ss}).

Q-T interval

- Nevertheless, drug effect on the QT was estimated on uncorrected QT, on QT corrected with Fridericia equation (QTcF) and using a population /subject slope correction (QTcss).
- Rufinamide concentrations were individual predictions from the one-compartment disposition model, at the time of ECG measurements.
- The base QT model was the sum of the population baseline QT and the population correction for the RR value (specific correction used RR=60/HR).
- The effect of time in the study, confounded with the placebo effect was better described by a saturable E_{max} model
- Rufinamide effect on QT was proportional to concentrations: within the range of concentrations observed and predicted, the decrease of QT was linear.

$$QTc_{ss} = \theta_1 + \left(\frac{\theta_3 \cdot TIME}{\theta_4 + TIME}\right) + \theta_6 \cdot CONC + \eta_1$$

$$COR = \theta_2 + \theta_5 \cdot TIME + \eta_2$$

$$QT = QTc_{ss} + COR \cdot 1000 \cdot (1 - RR)$$

Covariate model:

- The effect of demographic covariates age, sex, and weight was investigated on baseline, time effect and rufinamide effects as appropriate
- No covariables were added to the final model

Random effects model:

- A constant additive error was used
- Between-subject random effects were explored on all parameters. An additional model was preferred.

The parameters estimates, standard error of the estimate (SEE) and the %CV for the between-subject variability are summarized in Table 2 and 3.

Heart rate and QT interval data: observations, population and individual predictions, subject specific R-R correction, examples of 2 subjects are presented Figures 2 and 3.

Parameters	Estim	SEE	
Fixed Effects			
HR= θ_1 + θ_2*TIME / (θ_4+TIME) + θ_3*CONC+ η_1			
θ_1 HR intercept (bpm)	64.1	1.76	
θ_2 Maximum increase of HR due to placebo/time	15.4	1.98	
θ_4 Time for ½ maximum increase due to placebo/time (h)	116	31.7	
θ_3 Slope of rufinamide concentration effect	0.182	0.0552	
Random effects			Variability
Between-subject variance / additive error			
ω^2 η_1	65.7	15.7	SD 8.1
Additive residual error			
σ^2	36.4	2.37	SD 6.1

Table 2: Heart rate PKPD model and parameters
TIME: time in hours from 1st ECG, CONC rufinamide predicted concentration in μg/mL

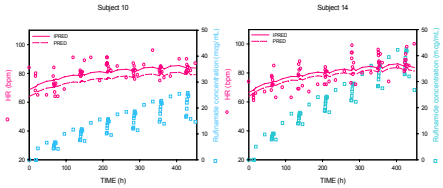

Fig. 2: Heart rate data: observations, population (PRED) and individual predictions (IPRED), examples of 2 subjects

Parameters	Estimate	SEE	
Fixed Effects			
QTcSS= θ_1 + θ_2*TIME / (θ_4+TIME) + θ_6*CONC + η_1			
COR= θ_2 + θ_5 *TIME + η_2			
QT = QTcSS + COR*1000*(1-RR)			
θ_1 Population baseline QT (ms)	395	4.68	
θ_2 Population RR correction	-0.138	0.00756	
θ_3 Maximum effect of placebo/time (ms)	-18.2	3.47	
θ_4 Time for ½ maximum decrease due to placebo/time (h)	39.5	8.91	
θ_5 Placebo / time change of RR correction	7.65E-05	1.93E-05	
θ_6 Slope of rufinamide concentration effect	-0.501	0.0929	
Random effects			Variability
Between- subject variance / additive error			
ω^2 η_1	260	60.2	SD 16.1
ω^2 η_2	4.08E-04	1.75E-04	SD 0.0202
Additive residual error			
σ^2	49.9	4.49	SD 7.1

Table 3: QT modelling with study/subject specific RR correction: QTcss analysis
TIME: time in hours from 1st ECG, CONC rufinamide predicted concentration in μg/mL

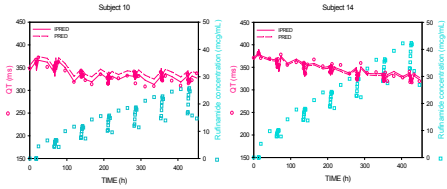

Fig.3: QT data: observations, population (PRED) and individual predictions (IPRED), subject specific R-R correction, examples of 2 subjects

Conclusion

- A one compartment disposition model was used to predict the rufinamide concentration.
- PK variability between subjects was very low and even with such a small sample size.
- Bioavailability decreased as dose increased according to an E_{max} model.
- Heart rate increased with time in the study and rufinamide concentrations.
- Rufinamide produce a small decrease in QTcss, proportional to rufinamide concentration.
- The cardiovascular tolerability was excellent.

References

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