Understanding the variability in clinical response to rufinamide, a new antiepileptic drug: a pooled PKPD analysis

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Introduction

Rufinamide is a new chemical entity developed for the treatment of epilepsy that modulates the activity of sodium channels, prolonging their inactive state. In phase II and phase III studies, rufinamide significantly reduced seizure frequency.

Objective

The objective of this analysis was to describe the exposure response (ER) relationship in patients with epilepsy (paediatric patients and adults) across a variety of doses, formulations, and concomitant anti-epileptic medications, over 10 years of development (1990-2000).

Data characteristics

• Data from 7 Phase II/III rufinamide studies were pooled: AE/PT2 , AE/ET1, CRUF331 0027, 0018, 0021A&P, 0016, and 0022.

• Studies were multicentre, double-blind, placebo-controlled (except for 3 studies), randomised, parallel-group, in patients with partial seizures, generalised seizures, and Lennox-Gastaut syndrome.

• Formulations and strength used in clinical trials varied during development:
  – Initially (studies AE/ET1, AE/PT2, and 0027), 100 and 200 mg roller dry compaction tablets (RC) were used,
  – Later (studies 0027, 0018, 0021, 0016, and 0022), when higher tablet strength was needed (400 mg), the process was changed to wet granulation process (WP).

• 50% of concentration data were obtained after administration of the RC tablet, with rich sampling design.

• 50% of concentrations were obtained after administration of the WP tablet with pseudo-randomly sparse sampling design.

• The range and median total daily dose administered per kg BW was much larger in WP studies than in older RC studies: 2.1 to 86.4 mg/kg versus 2.0 to 37.2 mg/kg.

• No children in the age range 2 to 11 years were recruited in the studies with RC formulation (AE/ET1 and AE/PT2).

• Benzodiazepines, barbiturate-type inducing agents (phenytoin, phenobarbital and primidone) and vigabatrin were more often administered as concomitant AED in the older (RC) studies, whereas topiramate and lamotrigine were more frequent in the more recent (WP) studies.

• Valproate was administered more often in paediatric than adult populations.

• TID dosing regimen was used in only one study of the pool: study 0016.

• Non-white subjects provided data only in the more recent studies (0016, 0018, 0021, 0022) using the WP formulation. Race was frequently not recorded in trials that used the RC formulation.

• Baseline total seizure frequency differs between study 0022 (Lennox-Gastaut syndrome) and all other studies.

Methods

• In 6/7 studies, the clinical endpoint was seizure frequency, whereas one study endpoint was the time to meet one exit criteria (study 0016).

• Data were standardised across studies and pooled to produce a single dataset for PK, and each PKPD analysis.

• Posthoc estimates of individual parameters and actual dosing history were used to predict subjects' exposure. C_{avss} was used for the PKPD analysis. Placebo subjects were given concentration value 0.

• The analysis of total seizure frequency was performed after Log_e transformation of frequency per day. When the seizure frequency was zero, a value of 1 seizure/28 days was imputed before log-transformation.

• The PKPD model included a disease/placebo effect, rufinamide exposure effect and selected covariates.

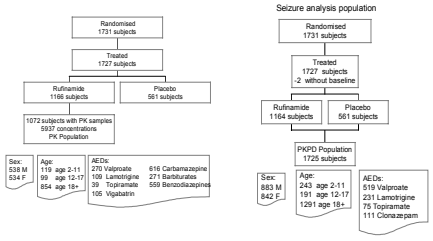
• Population PK and PKPD modelling used NONMEM. First Order estimation method was used for the PK, and First Order Conditional Estimation method was used for the PKPD.

DATA

Table 1. Disposition of subjects across clinical studies

Study	Patients randomised	Patients treated		PK population	PKPD population
		Rufinamide	Placebo		
AE/ET1	647	514	133	471	641
AE/PT2	50	50	NA	50	50
CRUF331 0016	142	142	NA	128	142
CRUF331 0018	155	78	75	68	155
CRUF331 0021A	313	156	157	144	313
CRUF331 0021P	269	136	132	130	269
CRUF331-022	139	74	64	65	139
CRUF331 0027	16	16	NA	16	16
All	-	-	-	1072	1725

Table 2. Subject's accountability for PK, and seizure frequency PKPD population



PK results

• Rufinamide pharmacokinetics is described by a one-compartment disposition PK model. Significant covariate effects are described in Table 3.

• Concomitant administration of lamotrigine or topiramate does not affect rufinamide pharmacokinetics.

• Rufinamide pharmacokinetics is not influenced by laboratory markers of renal or liver function, and by age.

• The predicted exposure is not different between the White and Black populations.

• The intersubject variability on PK parameters is moderate: 46.3% on clearance and 49.8% on volume of distribution.

Table 3. Significant covariate effect on pharmacokinetics of rufinamide

Absorption	Ka=0.624h^{-1} for the RC tablet. Ka decreases with increasing dose
	No absorption phase could be described from the sparse sampling studies (WP formulation)
Bioavailability	Greater for WP formulation than RC tablet, with relative bioavailability of 0.538. Both formulations decreases with increasing dose
CL	Proportional increase with BSA
	Slightly less in female than male patients
	Decrease associated with valproate, resulting in increased predicted concentrations by 55 to 70% in children, 23-26% in adolescents and less than 16% in adults
	Increase with co administration of phenytoin, phenobarbital or primidone leading to decrease of rufinamide concentrations by 43-46% in children, 30-32% in adolescent and 25-26% in adults
	Increase with co administration of carbamazepine or vigabatrin leading to decrease of rufinamide concentrations by less than 30% overall
V	Increase with BSA (power function)
	Adolescent had a larger volume of distribution

Seizure frequency PKPD results

• The natural logarithm of total seizure frequency is described by the sum of an intercept (baseline frequency- prior to treatment initiation and at zero concentration of rufinamide), the placebo effect with time in the study (constant decrease throughout the study) and a decrease proportional to rufinamide concentrations. Results are given in Table 4, and in Figure 1.

• The intercept (baseline) is larger for study 22 (Lennox-Gastaut syndrome), in children (2-11yr) and in patients with concomitant clonazepam treatment.

• The placebo effect is constant throughout the treatment period. It is not affected by age and sex. Patients with concomitant lamotrigine have less placebo effect during treatment.

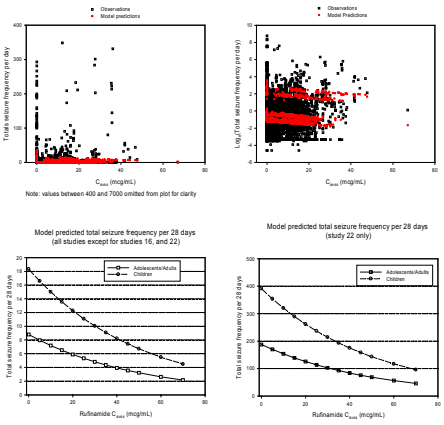
• The rufinamide effect is not affected by concomitant AED, age and sex of the patients. The slope of effect of rufinamide concentration does not differ between the various other populations entered into in the studies: inadequately controlled primarily generalised tonic-clonic, simple partial, complex partial secondarily generalised, Lennox-Gastaut syndrome seizures.

Table 4. Population PKPD model for Log_e(total seizure frequency)

Parameters	Estimate	SEE	95% CI	Variability
Log_e(total seizure frequency)= **θ_0+θ_1 (if study 22) + θ_2 (if age 2-11 yr)+ (θ_3*CCLO) or (+ θ_3*clonazepam=Y))** **+ θ_4 (nday>0) + θ_5 (nday>0 and lamotrigine =Y)** **+ θ_6*θ_7/TID/ C_{avss}**				
θ_0: Intercept	-0.984	0.0306	[-1.024; -0.904]	
θ_1: Increase for study 22	3.06	0.126	[2.81; 3.31]	
θ_2: Placebo (shift for nday>0)	-0.193	0.0212	[-0.235; -0.151]	
θ_3: Slope of C_{avss} (rufinamide effect)	-0.0201	0.003	[-0.026; -0.0142]	
θ_4: Children (2-11 yr)	0.734	0.108	[0.522; 0.946]	
θ_6: Slope of clonazepam concentration effect	0.00995	0.00378	[0.00254; 0.01736]	
θ_7: Clonazepam Y/N (studies 16 & 27 only)	2.40	0.725	[0.98; 3.82]	
θ_8: Study 16 (TID) on rufinamide effect	0.027	0.0041	[0.018; 0.036]	
θ_9: Lamotrigine Y/N	0.200	0.0534	[0.095; 0.305]	
Random effects				
ω^2_1: intercept (additive error)	1.41	0.0606	[1.29; 1.53]	SD 1.2
ω^2_2 slope C_{avss} (proportional error)	0.940	0.188	[0.572; 1.308]	CV 97%
σ^2 (additive residual error)	0.606	0.0175	[0.572; 0.640]	SD 0.8

CCLO: clonazepam concentration; TID=1 if Study 16, Otherwise TID=0

Figure 1. Observed, and model predicted effect of rufinamide on total seizure frequency



Conclusions

• Despite the limitations due to data characteristics, the data were very rich and the analysis method sensitive enough. The main features of this integrated PKPD model represent accurately the data.

•This integrated PKPD model allowed a complete bridging between formulations/doses, and a complete bridging between populations (adults and children) over 10 years of development.