Regarding the immunotoxic potential, the review of the findings indicate that these changes do not appear to be inn favour of a direct effect of rufinamide, although this cannot be exclude. Therefore, this potential will be monitored in the post-authorisation phase as describe in the risk management plan

Treatment-related increases in the incidences of benign thyroid follicular adenomas were observed in males at 60 and 200 mg/kg. This tumour is caused by the effect on the pituitary-thyroid axis, also observed in the repeated-dose toxicity studies. The disruption of the pituitary-thyroid axis is a well known rat specific phenomenon and thus lacks clinical relevance.

In the toxicokinetic study only plasma concentrations from the cancer study in rats are given, no AUC-values are calculated. At 200 mg/kg, the AUC is estimated to be approximately 3600 µmol·hr/L. The AUC-levels give a margin to maximum clinical exposure of approximately 2.

- Reproduction Toxicity

Fertility and early embryonic development
In the male rat no adverse effects on fertility parameters were seen at up to 150 mg/kg. Testis weight was unaffected by treatment, however, no histopathology on testis were performed. Histopathology on male genital organs, including testis, was performed in the rat carcinogenicity study and in the 26/52 week repeated-dose toxicity study, and no adverse effects were recorded. In female rats, no effects on fertility parameters were seen at up to 150 mg/kg. An increase in post-implantation losses and still births was seen at the high dose, together with signs of maternal toxicity. For males in the F_0 generation NOAEL was 50 mg/kg, for females no NOAEL was established, for F_1 pups, the NOAEL was 15 mg/kg.

Embryo-fetal development
In rats, there was no evidence of teratogenic potential after 300 mg/kg. The skeletal anomalies and variants seen in F_1 generation are considered due to a retardation of ossification along with the decrease of fetal body weight. These findings were seen at doses with signs of maternal toxicity in all dose groups. The NOAEL for F_0 dams was not established, in pups NOAEL was 20 mg/kg.
In rabbits, no evidence of teratogenic potential was seen. The skeletal variations and decreased fetal weights occurred at dose levels where dams showed reduced food consumption and decreased net body weight gain, thus the effects are considered due to maternal toxicity. NOAEL for dams and pups was 30 mg/kg. In rabbits, no AUC-levels were submitted. In toxicokinetic study 76/1987, plasma concentration after repeated-dosing with 200 mg/kg was 115 µmol/L, which gives an exposure approximately the same as maximum clinical exposure (C_{max}).

Prenatal and postnatal development, including maternal function
In mice, administered up to 500 mg/kg from gestation day 15 to lactation day 20, no adverse effects on any of the maternal or pup parameters evaluated were seen. The NOAELs for maternal toxicity and for the offspring were both 500 mg/kg. The margin to maximum human exposure is approximately 1.5
In rat, three peri-postnatal studies were conducted. In two cross-fostering studies rufinamide was administered at a dose of 150 mg/kg from gestation day 15 to day 21 of gestation or day 14 of lactation Treated dams displayed decreased food consumption and body weight parameters. A slight decrease in pup weight and pup survival at birth and on lactation day 0-4 was seen mainly in *in utero* treated pups and not cross-fostered, and in *in utero* treated pups and cross-fostered to untreated dams.
In study 997078, rats were dosed with up to 150 mg/kg from gestation day 6 to day 20 of lactation.
At 150 mg/kg, CNS related symptoms and affected body weight parameters were seen in the dams. At the same dose, an increase of pup mortality and pup weight per litter was observed on day 1 to 21 of lactation. There were no treatment-related effects on the other parameters studied, including postnatal development. The NOAEL in this study was 30 mg/kg for the F_0 females and for the F_1 offspring.
In conclusion, the effects seen on fetal weights and survival are considered related to maternal toxicity, affecting the fetuses *in utero*.

Distribution studies in pregnant rats and rabbits
Distribution studies indicated that the embryo/fetus was exposed to rufinamide throughout the period of organogenesis in the embryo-fetal development studies. In both rats and rabbits distribution was also seen to the mammary glands suggesting that rufinamide and/or its metabolites would be excreted with the milk. Therefore, breast-feeding is not recommended as stated in the SPC section 4.6.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
In rats (dose-range finding study), pups were dosed from days 7 to 21 *post partum* or to day 35 *post partum*. Tubular dilatation in the renal medulla, associated with mineralization, of one animal at 60 mg/kg and in several animals at 200 and 600 mg/kg was seen.
In the pivotal study, where the animals were dosed at maximum 150 mg/kg for up to 10 weeks, decreased activity and pup weights, increased relative liver weights, centrilobular hepatocellular hypertrophy and pituitary cytoplasmic vacuolation was seen. All other parameters were unaffected by treatment. The NOAEL was 15 mg/kg. It can be concluded that, in studies with juvenile rats, no additional toxicity was seen than was already known from repeated-dose studies performed in adult animals. The adverse effects in the kidney seen in the dose-range finding study, was also seen in the carcinogenicity study and in repeated-dose toxicity study 92-100 in rat.

In Beagle dogs, two studies using juvenile animals were conducted. In the pivotal study, where dogs were dosed at maximum 200 mg/kg for 13 weeks, soft faeces, hepatic pigment accumulation was seen. The NOAEL was considered to be 5 mg/kg, in view of the treatment-related increase in ALT and histopathological findings in the liver at 200 mg/kg. Systemic exposure in young and mature dogs was similar for the same mg/kg dose. There was no margin to the maximum clinical exposure; at the NOAEL set in the juvenile studies, 5 mg/kg, the exposure is 0.03 and 0.05 for males and females, respectively, of maximum clinical exposure.

In conclusion, regarding the reproductive toxicity studies, no indications of rufinamide being teratogenic was seen. Reproductive toxicity (postimplantation losses and stillbirths) was seen at doses where maternal toxicity was observed. In juvenile rats and dogs the target organs were liver and kidney, as seen in adult animals. Rufinamide did not cause any adverse effects on postnatal development. The NOAELs reached in all the reproductive toxicity studies, do not leave any margins to human maximum exposure. Thus, the reproductive toxicity studies are considered insufficient to establish the safe use of rufinamide in humans during pregnancy.

- Toxicokinetic data

An overview of the toxicokinetic data and the exposure ratio in comparison to children human exposures is given in the table below:

Table 21 Notable changes in the pivotal repeat-dose toxicity studies and comparison with drug exposure in children.

Species	Noteworthy findings	Dose (mg/kg)	$AUC_{(0\text{-}24\ hr)}$ (µmol hr/L)		$AUC_{(0\text{-}24\ hr)}$ ratios to human exposure*	
			Male	Female	Male	Female
Rats	None (NOAEL)	20	NP	NP	NP	NP
	Reduced body weight gain and food consumption. Increased T4, Histopathological changes in liver, pituitary and thyroid	200	4320	3652	3.4	2.9
Dogs	Histopathological changes in liver	20	734	352	0.6	0.3
	Increased ALP	200	991	3580	0.8	2.8
Cynomolgus monkeys	None (NOAEL)	60	1690	2290	1.3	1.8
	Increased AST and ALP Histopathological changes in liver Cholelithis	200	3190	3060	2.5	2.4

NP = not performed
* Human exposure levels in children aged from 2 years old of the most usual clinical use was 45 mg/kg (1272 µmol hr/L).

- Local tolerance

A local tolerance test was conducted in rabbit. No skin irritating effect was seen after up to 72 hours.

- Other toxicity studies

Antigenicity/contact hypersensitivity studies

An antigenicity/contact hypersensitivity test was performed in guinea pigs. No reactions were observed and the sensitization rate was 0%.

Dependence studies

Two dependence studies were conducted in Cynomolgus monkeys. No withdrawal signs were seen after 200 or 400 mg/kg administered over a 28-days period and no monkeys self-administered using intragastric self-injection at doses of 5-20 mg/kg. From the tests performed it can be concluded that rufinamide did not show dependence liability.

Ecotoxicity/environmental risk assessment

An ecotoxicity/environmental risk assessment has been performed by the Applicant. Considering the extensive human metabolism, low water-solubility, and otherwise low ecotoxic potency of rufinamide the CHMP supports the conclusion that the environmental risk is negligible.

Discussion on the non-clinical aspects

In vitro, rufinamide is involved in modulation of sodium channels probably by prolonging their inactive state and has demonstrated efficacy in relevant *in vivo* models of seizure disorders.
The behavioural and safety pharmacology studies carried out show that rufinamide is without unwanted pharmacological effects at doses exceeding those which confer anti-convulsant protection.

Rufinamide shows a low acute toxicity. In the repeated-dose toxicity studies, the main target organ was the liver. Rufinamide did not show genotoxic potential. There is no evidence of teratogenic potential in either rat or rabbit, but showed reproductive toxicity at doses where maternal toxicity was seen.
The juvenile toxicity data for rat and dog indicate that the juvenile is not more sensitive than the mature animal to the toxicity of rufinamide. In addition, the rat study showed no effects on behavioral and physical development.

Regarding the immunotoxic potential, decreased bone marrow cellularity (dogs/rats), lymph nodes (dogs/baboons) and spleen (baboon) were observed inconsistently in repeat-dose toxicity and carcinogenicity studies. No relevant findings have been detected in the clinical trials. However, clinical hematological adverse events will be monitored in post-authorisation as part of the pharmacovigilance risk management plan.

Concerning the carcinogenicity aspects, in the mouse, increases in hepatocellular adenomas and carcinomas and in incidence of osteomas in both sexes at the high dose were observed. Treatment-related myelofibrosis was also seen at mid and high dose in both females and males in mice.
The mechanism of this myelofibrosis remains unknown. Nevertheless, this is regarded as part of fibro-osseous lesions (FOL), which is thought to be age dependent. In this particular case, regarding the hyperostosis and osteomas, the increased exposure to fluoride and mouse-specific retro-virus are contributing factors. Therefore it is probably not predictive of development of myelofibrosis in human. In any case, the risk of myelofibrosis will be monitored in the risk management plan

Rufinamide shows no physical or overt psychological dependence liability in cynomolgus monkey.
Rufinamide showed no skin irritation, corrosive or sensitization potential in the skin irritation study in rabbit and in the contact hypersensitivity study performed in guinea pigs.
There are no safety-related concerns with respect to impurities, degradation products and excipients.
The environmental exposure resulting from the limited use of the product will be low.

4 Clinical aspects

Introduction

Pharmacokinetics studies have been completed to acceptable, contemporary standards, and in accordance with GCP.
Clinical studies initiated prior to the effective date of GCP regulations were conducted in accordance with the relevant standards at the time.
According to the report the sponsor claimed all clinical studies initiated after 1995 were conducted in accordance with the principles of GCP and Since January 1997, all studies have been in compliance with ICH guidelines on GCP (CPMP/ICH/135/95).

As only one pivotal study was performed to support this Marketing Application, an inspection was requested and performed in two sites, one in US and one in Europe. The conclusion was that the recorded and reported data of the inspected sites seem to be trustworthy and reliable to the inspectors.

All clinical studies initiated after 1995 were conducted in accordance with the principles of GCP. Since January 1997, all studies have been in compliance with ICH guidelines on GCP (CPMP/ICH/135/95). Studies initiated prior to the effective date of GCP regulations were conducted in accordance with the relevant standards at the time.

Pharmacokinetics

The overall clinical pharmacology program of rufinamide consists of 23 studies, including 353 healthy subjects and 25 patients, treated either with rufinamide or placebo or both. Twenty-two (22) studies were conducted with healthy subjects, one study including also patients with renal impairment. One study was conducted in paediatric patients with epilepsy Additionally, pharmacokinetic information from clinical efficacy and safety studies were included in a population pharmacokinetic/pharmacodynamic (PKPD) analysis. The PK population included 1072 patients and PD population 1725 patients.

- ***Analytical methods***

Rufinamide concentrations were measured in plasma and in urine collected from healthy subjects during the bioavailability, bioequivalence and clinical pharmacology studies. Rufinamide was also measured in plasma following rufinamide administration in all the pivotal clinical trials, i.e. in 10 clinical studies conducted between 1991 and 2004.
Different analytical methods for the measurement in biological samples of rufinamide were developed and validated throughout the human clinical development of rufinamide either in Europe or in the United States and cross-validated between the two sites. Eight bioanalytical methods have been validated for the assay of rufinamide (and its main metabolite CGP47292) in different human matrices (plasma and urine).
Until 2004, all methods consisted in HPLC with UV detection. Initially, the methods involved manual extraction. Later, automated extraction was developed using robotic systems. The analysis range were approximately 25-2000 ng/ml for 0.5ml plasma and 125-1000 ng/ml for 0.1ml urine (FR) or 50-4000ng/ml (USA). Accuracy and precision were generally satisfactory.

In 2004, a LC/MS/MS method was developed. The calibration range was 20 to 20000ng/ml. The bias was less than 2% and the precision had CV<5.3% in samples. The extraction used protein precipitation; the HPLC was reverse phase liquid chromatography. The method was used for analysis of samples in the most recent study in healthy subjects (E2080-A001-001) over a dose range of 800 to 7200 mg per day multiple doses.

- ***Absorption***

Rufinamide is chemically stable and neutral in solution. The solubility in water as well as in gastric and intestinal fluid is low. Rufinamide has a slow absorption with a Tmax of about 4-7 hours. In a population PK analysis of the data from study E2080-A001-001 (using a one-compartment first-order absorption and elimination), the absorption constant (Ka) was estimated to 0.21 h^{-1} and the absorption half-life to 3.4 hours. The absorption would then still endure for 12 hours and thus affect the "model-

independent" estimations of the terminal half-life. This is roughly in line with a Wagner Nelson analysis performed which showed that the dose is absorbed in 9 hours.

Active apical to basolateral transport of rufinamide has been observed in Caco-2 cells. The metabolite CGP47292 has been found to be actively secreted from the basolateral to apical side of the membrane (ie out to the intestinal lumen). Rufinamide was not metabolised to CPG47292 during its transport from the apical to basolateral compartment. Data indicate that rufinamide is not a substrate for P-gp, but but the role of other transporters such as OATP-B, implicated in the uptake of some (mainly acidic) drugs from the intestinal lumen, cannot be excluded.

Bioavailability
The absolute bioavailability of rufinamide has not been determined in man due to the low aqueous solubility of the drug. The mean fraction of the dose recovered in urine, mainly as metabolite CPG47292, was 82% indicating that at least this part of the dose is absorbed in some form.
The bioavailability is less than dose-proportional with increasing dose (see section "dose proportionality").

Comparison of trial formulations with finished product
During clinical development, several oral formulations were evaluated in healthy subjects and in patients. Tablets in strengths of 50, 100 and 200 mg were produced using a roller dry compaction method (RC) and are referred to as the Clinical Service Form (CSF). These tablets were used in approximately half of the clinical studies in healthy subjects and in three efficacy and safety studies in patients, at doses of up to 3200 mg per day.
Later, when a higher tablet strength was needed (400 mg), the process was changed to wet granulation (W) and to wet granulation with a pre-densification step (WP). These tablets are referred to as the Final Market Image (FMI). The FMI tablet had a different composition than the CSF tablet and is the formulation to be marketed. The FMI tablet is film coated to mask the slightly bitter taste. FMI tablet strengths of 100, 200 and 400 mg have been used in all the remaining clinical pharmacology studies and in 5 clinical and efficacy studies in patients with epilepsy, including the pivotal clinical study 022.
An oral suspension formulation was developed and evaluated in healthy subjects. However, no suspension is available for market use in young children. The applicant committed to develop such a formulation for children in the post-authorization phase (see follow-up measures)

Two 200 mg CSF tablets, were compared with one 400 mg FMI film-coated tablet under fed and fasting conditions. The results (Table below) indicate that concomitant food intake improved the bioavailability of the 400 mg tablets significantly. The FMI 400 mg and CSF 200 mg formulations were not bioequivalent as the FMI tablets gave higher AUC and Cmax of rufinamide. In a bioequivalence study, the FMI formulation, gave 20% higher AUC the CSF formulation under fed conditions. In the large population pharmacokinetic analysis, the FMI table was estimated to give a 86% higher AUC than the CSF tablet (see further section population PK).

Pharmacokinetics of rufinamide after administration of the 400 mg FMI and 200 mg CSF formulation (mean±SD and median for Tmax) Study 037

	CSF fed 2*200mg	FMI fed 400mg	FMI fasted 400 mg	90%CI of mean ratio: FMI/CSF
$AUC_{0-\infty}$ (ug*h/ml)	69.85±13.55	84.33±13.84	63.25±14.61	1.16-1.26
AUC_{0-last} (ug*h/ml)	68.63±13.16	83.10±13.33	61.78±14.34	1.16-1.27
Cmax (ug/ml)	3.30±0.37	4.42±0.57	2.85±0.52	1.27-1.41
Tmax (h) median	6.00	4.00	6.00	

Influence of food
Food increases the bioavailability (AUC) of rufinamide by approximately 34% and the peak plasma concentration by 56% when administered as the FMI formulation, which was used in the pivotal clinical study. Therefore, it is preferable to administer rufinamide with food as reflected in the SPC.

- ***Distribution***

Rufinamide is 30% bound to plasma proteins. The apparent volume of distribution is about 75 L (population estimate) and increases with increasing body surface area and is larger in adolescents.

- ***Elimination***

Metabolism

Rufinamide has a terminal half-life of about 10 hours and is eliminated by metabolism.

After a radiolabelled dose, the radioactivity observed in plasma almost completely consists of rufinamide and the metabolite CPG 47292. The main part (82%) of the AUC of radiolabelled compounds consisted of rufinamide. CPG 47292 contributed to approximately 13% of the AUC of radiolabelled compounds. The half-lives of radioactivity, rufinamide and CPG 47292 were very similar (9 vs. 8 hours).

The main metabolic pathway is catalyzation by carboxylesterase(s) (CES) which hydrolyzes the carboxyl amide group leading to the formation of CGF 47292, an acidic and pharmacologically inactive derivative. CES enzymes are present in the liver but also in other tissues including the brain. Minor metabolites were formed by glucuronidation of CGP47292.

Cytochrome P450-mediated metabolism is very minor. *In-vitro* studies showed that rufinamide had little or no significant inhibitory capacity for the following human P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11-2.

In cynomolgous monkeys and mice, a glutathione conjugate is being formed. During its formation fluoride ions are released. This pathway has been associated with cholelithis and osteomas in preclinical studies. It cannot be completely excluded that glutathione conjugates are formed in human but if so, the amounts are small. This is reflected in the SPC.

Excretion

CGP47292 is an anion at physiological pH and is excreted largely in urine. The mean fraction of the dose recovered in urine, mainly as metabolite CPG47292, was 82%. Only 2% of the dose was found in urine in unchanged form the first 48 hours after dosing.

- ***Dose proportionality and time dependencies***

Rufinamide shows dose-dependent pharmacokinetics with less than proportional increased in exposure with dose. The dose-dependency is present for all studied formulations. The pharmaceutical documentation indicates that this is related to the poor water solubility. The rate of dissolution was lower when the dose to be dissolved increased.

It may also be related to the active in-transport of rufinamide in the intestine indicated by in vitro assays. The dose-dependency is present within the therapeutic dose range.

The pharmacokinetics of rufinamide was studied after a 400 mg single-dose and after administration of 400 mg b.i.d under fed conditions for 4.5 days to young and elderly healthy volunteers. A slight decrease in exposure/increase in oral clearance was seen also in this study (see following table)

Table:Single and multiple dose pharmacokinetics of rufinamide (400 mg vs 400 mg b.i.d.)

	Single dose			Multiple dose			
	Cmax (ug/ml)	Tmax (h)	AUC0-∞ (ug*h/ml)	Cmax (ug/ml)	Tmax (h)	AUC0-12h (ug*h/ml)	T1/2 (h)
Elderly	4.6±1.1	6.0±2.1	84.5±23.5	7.6±1.5	3.9±2.4	66.2±10.3	8.3±1.1
Young	4.2±0.7	6.6±1.9	81.0±18.8	7.5±1.1	46.1.5	72.3±1.5	10.2±2.4

The pharmacokinetics of rufinamide does not appear to be markedly time-dependent. Non or a small increase in oral clearance was seen under multiple-dose conditions.

- Target population

Children

The target patient population mainly includes children. However, there are few full pharmacokinetic profiles in paediatric patients. Instead, the applicant has performed a population pharmacokinetic analysis including both adult and paediatric patients. Simulations have been submitted showing predictions of the exposures resulting from the recommended doses in different bodyweight ranges. The median systemic exposure is predicted to be 33% higher in patients with a bodyweight <30 kg as compared to the remaining patients. The variability was also higher resulting in 95% percentile exposure more than double as high as in the other patient groups. The main clinical efficacy and safety data has probably been collected in patients weighing more than 30 kg.
At the request of CHMP, the applicant further discussed which dose is the most suitable in the patients weighing under 30 kg using simulation model evaluation plots and further population PK analysis plotting the frequency distribution of ages and weights in the population (See Population PK analysis).

Special populations

Liver and renal impairment

The pharmacokinetics of rufinamide was not altered in patients with impaired renal function. Dialysis, resulted in a 12% decrease in exposure and therefore do not require dose adaptation. No study has been performed in patients with liver disease. Severe hepatic impairment is contraindicated.

Other populations

No clinically relevant differences related to sex, race or the elderly were noted in population PK analyses.
There were some outliers (4 in the studied population) with many-fold higher rufinamide exposures than the remaining patients. No reason for this has been identified and the applicant is encouraged to further investigate this post-marketing (e.g. genetic polymorphism of carboxylesterases)

- Population PK analysis

The dose of rufinamide is titrated after clinical response. The effect of several variables will be compensated for by the titration if performed sufficiently slowly. However, the effect of external factors such as concomitantly used drugs, as well as changing organ function may need dose-adjustments during treatment and is of importance. Also, the dose-titration method was investigated to be suitable for patients over the large age and weight range intended for treatment.

The results show that the median systemic exposure is predicted to be 33% higher in patients with a bodyweight <30 kg as compared to the remaining patients. The variability was also higher resulting in 95% percentile exposure more than double as high as in the other patient groups.
Also, in the absence of valproate, dosing children <30 kg with different BMI up to 800 mg results in similar exposure, showing that the effect of body size is very limited. Therefore, a dose regimen in adpted in the SPC according to these parameters (body weight, concomitant use of valproate)

However, the effect due to valproate cannot be assessed fully due to the way the covariate effect was modelled. A new analysis has been requested by CHMP as a post-marketing commitment and depending on the results a new study PK study may need to be performed in order to investigate the effect of valproate on rufinamide pharmacokinetics in paediatric patients (up to 12 years). At present, the proposed new maximum dose of 400 mg/day is considered satisfactory.

Finally, in the SPC, the recommended dose range is 200 mg to 1000 mg/day in patients weighing less than 30 kg. In patient receiving valproate, the maximum recommended dose is 400 mg/day (see above and PK interactions). The proposed recommended dose range is 400-1800, 400-2400 and 400 – 3200 mg/day in children and adults weighing 30-50, >50-70 and >70 kg, respectively.

- Pharmacokinetic interaction studies

Rufinamide did not inhibit the main cytochrome P450 enzymes *in vitro*. The drug is a mild to moderate inducer of CYP3A4. Treatment with rufinamide 400 mg b.i.d. resulted in a 55% increase in triazolam clearance. The effect may be more pronounced at higher rufinamide doses.. It cannot be

excluded that rufinamide may also decrease the exposure of drugs metabolized by other enzymes, or transported by transport proteins such as P-glycoprotein.

In the present treatment of LGS, usually valproate is combined with a benzodiazepine and one of the never AEDs (lamotrigine and topiramate). Thus, rufinamide is likely to be combined with these drugs.

Rufinamide moderately reduces the plasma concentrations of phenobarbital but give a moderate increase in the plasma concentrations of lamotrigine and carbamazepine. These moderate effects are considered to be non-clinically relevant. Not effect on the clearance of topiramate (P-gp substrate) was noted after repeat dosing of rufinamide. However, since rufinamide may significantly decrease phenytoin clearance and increase average steady state plasma concentrations of co-administered phenytoin (by 0-50% in children, less pronounced in adolescents and adults), consideration should be given to reducing the dose of phenytoin. This is reflected in the SPC.

Valproate increases the exposure of rufinamide. The most pronounced increases were observed in smaller patients of low bodyweight (<30 kg). The need for adjustment of rufinamide dosages is mentioned in the SPC (see above discussion inPopulation PK section).
The plasma concentrations of rufinamide are decreased by phenytoin and other barbiturates, such as carbamazepine and primidone. This is mentioned in the SPC. The active in-transport of rufinamide is inhibited by both phenytoin and valproate *in vitro*. The mechanism of interaction is presently unknown. Possible explanations include CES inhibition or efflux transporter inhibition.

Pharmacodynamics

- Mechanism of action

The primary *in vitro* pharmacodynamic data indicate that rufinamide interacts with the inactivated state of the sodium channel and slows conversion to the active state thereby reducing the frequency of action potentials in rat neurons, an effect that could contribute to blocking the spread of seizure activity from an epileptogenic focus. However, the exact mechanism of action is not clear.

- Primary and Secondary pharmacology

In vitro studies have revealed that rufinamide limits the frequency of firing of sodium-dependent action potentials in rat neurons, which could contribute to blocking the spread of seizure activity from an epileptogenic focus. Rufinamide was effective in a broad range of animal models of generalized tonic-clonic seizures and models of partial seizures (see non-clinical part). The relevance of animal models to human epilepsy is unknown.
Other pharmacological effects of rufinamide include an analgesic effect in models of neuropathic pain. Rufinamide has been investigated for its effects on hyperventilation related EEG. The drug did not affect EEG frequency and had no effect on hyperventilation related negative EEG-shift.

Concentration-response analyses in healthy subjects has demonstrated that rufinamide causes a small increase in heart rate, proportional to rufinamide concentration, e.g. heart rate is predicted to increase by 2.7 bpm at an average steady state concentration of rufinamide of 15 µg/ml. Rufinamide causes a small decrease in corrected QT, proportional to rufinamide concentration, of 0.50 ms per 1 µg/ml, which equates to a decrease of 7.5 ms at a typical 15 µg/ml rufinamide concentration in patients.

A single dose of 800 mg rufinamide administered to young subjects neither delayed nor reduced event-related potentials such as the N100 and the contingency negative variation (CNV), but rather increased the amplitude of the N100 ($p<0.05$). Reaction time was not increased. The drug did not affect EEG frequency and had no effect on hyperventilation related negative EEG-shift.
Nevertheless, the results do not allow concluding that rufinamide has less cognition impairing effects than other known AEDs. The possible impact on learning, intelligence, and also growth, endocrine functions, puberty and childbearing potential will be monitored in post-authorisation as described in the Risk Management Plan.

Relationship between plasma concentration and effect
Nonlinear mixed effects modelling using NONMEM was applied to explore the relationship between the total seizure frequency and the rufinamide exposure. From the final model it was concluded that the seizure frequency decreases proportionally to the exposure of rufinamide, expressed as average concentrations at steady state. The decrease in number of seizures was neither affected by the type of epilepsy nor treatment with other antiepileptic drugs. The PD simulation results show that the main reduction of total seizure frequency occurs during the first week of treatment.

Clinical efficacy

Nine double-blind (8 completed), controlled studies are included in this application to evaluate the safety and efficacy of rufinamide in epilepsy-related indications.
The pivotal study demonstrating the efficacy of rufinamide in the target population (as adjunctive therapy in children and adults with LGS) was Study 022, a double-blind, placebo-controlled, randomized, parallel group study.
This pivotal clinical study (study 022) has been planned and performed according to current standards and recommendations from guidelines for the treatment of epilepsy and in accordance with published study designs of other antiepileptic drugs in this indication. Nevertheless, the maintenance phase (10 weeks) is shorter than the recommended one (12 weeks) from the Note of Guidance on Clinical Investigation of Medicinal products in the Treatment of Epileptic Disorders (CPMP/EWP/566/98).

The other clinical studies performed between 1991 and 2001 provide supportive clinical information.
The supporting studies are :

- Studies AE/PT2, AE/ET1 and 021A : as adjunctive therapy in adults with refractory partial seizures,
- Study 021P : as adjunctive therapy in children with refractory partial seizures,
- Study 018 : as adjunctive therapy in adults and children with primary generalized tonic clonic (PGTC) seizures and,
- Studies 016 and 038: as substitution monotherapy or monotherapy for partial seizures in adults and adolescents.

A total of 1240 subjects received rufinamide and 635 subjects received placebo over a treatment period of up to 12 weeks.

Efficacy data from 3 open-label extension (OLE) studies are also provided: 1 in patients with LGS (Study 022E) and 2 in adults with partial seizures (Studies AE/ET1E and 021AE). A total of 758 subjects received rufinamide in these studies.

In addition several other uncontrolled studies were performed.

- Dose response study

Study AE/ET1 evaluated the efficacy of different rufinamide doses (200, 400, 800, and 1,600 mg/day) in patients with partial seizures on up to three concomitant antiepileptic drugs (AED).

- ***Methods***

This was a multicenter, double-blind, randomized, placebo-controlled, 5-arm parallel trial. The core trial consisted of a 3-month prospective Baseline Phase followed by randomization to a 3-month double-blind treatment phase. Were included in or out-patients, age 15-65 with inadequately controlled partial seizures with or without secondarily generalized seizures (i.e. 4 seizures/month during the 6 months prior to the Baseline Phase who were being treated with 1-3 concomitants AEDs at a constant dose for at least 4 weeks before the Baseline Phase. Additional criteria for randomization were compliant patients with at least 9 seizures during the Baseline Phase and no change in concomitant AED dose.

On entry to the double-blind treatment phase, patients were randomized equally to one of five treatments groups (200, 400, 800, and 1,600 mg/day or placebo). There were no dose titration. Treatment was administered orally in a twice-daily regimen.

The primary variable was the total seizure frequency per 28 days in the double-blind Treatment Phase.

A total of 647 patients met the inclusion/exclusion criteria, completed the 3-month prospective Baseline Phase, and were randomized to treatment. All 647 patients received study drug and were included in the intent-to-treat population. The median duration of therapy was 84 days (12 weeks) in each of the 5 treatment groups.
It should be noted that the included patients were adults with partial seizures which were not adequately controlled with standard AEDs. The type of epilepsy and the age of the patients are thus not representative for the applied indication, the Lennox-Gastaut syndrome, which occurs mainly in children.

- ***Results***

Primary efficacy variable: total seizure frequency per 28 days
Total seizure frequency per 28 days during the baseline and double-blind phases is summarized by treatment in the following table:

Table: Summary of total seizure frequency per 28 days (Study AE/ET1, ITT)

Treatment group	PLB	200 mg/day	400 mg/day	800 mg/day	1600 mg/day
Number of patients	133	127	125	129	133
Baseline seizure frequency mean/median (range)	36.28/11.67 (3.00-676.00)	24.32/11.07 (2.96-293.71)	23.84/11.84 (2.77-315.67)	28.12/12.67 (1.67-315.08)	26.94/11.33 (3.33-246.67)
Double-blind seizure frequency mean/median (range)	44.39/11.86 (0.00-1579.00)	25.11/11.00 (1.00-227.00)	21.54/10.67 (0.62-290.33)	26.43/11.00 (0.00-279.18)	26.16/10.67 (0.00-311.56)
Seizure frequency ratio mean/median (range)	1.13/1.05 (0.00/5.17)	1.08/1.01 (0.29-2.85)	0.97/0.93 (0.13-4.19)	0.96/0.88 (0.00-3.25)	0.98/0.87 (0.00-4.15)

*** Seizure frequency ratio is the seizure frequency per 28 days in the Double-blind Treatment Phase divided by that in the Baseline Phase.**

Cross-reference: Table 8.1.-1, Module III Tables 8.1.1.-1 - 8.1.1.-5, Module VI Data Listing 33

In conclusion; the minimum effective dose in adolescents and adults (15-65 years) in inadequately controlled partial seizures with or without secondarily generalized seizures appears to be 400 mg/d, administered as equally divided doses every 12 hours. The three doses 400, 800 and 1600 mg/day appear to be similarly effective in this study.

- Main study

The primary efficacy study in the development program is Study 022, a double-blind placebo-controlled adjunctive therapy study in the Lennox-Gastaut syndrome, with an open-label extension

METHODS

Study 022 was a multicenter, double-blind, placebo-controlled, randomized, parallel-group study.

Study Participants
Patients included in the pivotal study must have between 4 and 30 years, been on a fixed dose of one to three AEDs during the 28-day Baseline Phase, had a diagnosis of inadequately controlled seizures associated with LGS which included both atypical absence seizures and drop attacks (or other

nomenclature that defines identical seizure type such tonic-atonic or astatic seizures). Other seizure types may have included tonic, tonic-clonic or myoclonic. The diagnosis of LGS was based on the International League Against Epilepsy (ILAE) and confirmed with direct 6- to 24-hour video-EEG recordings, had at least 90 seizures in the month prior to the 28-day Baseline phase, had an EEG within 6 months prior to the baseline demonstrating a slow spike-and-wave pattern and a computed tomography (CT) scan or a magnetic resonance imaging (MRI) study, confirming the absence of a progressive lesion.
Patients with a treatable aetiology of seizures (active infection, neoplasm, metabolic disturbance), a history of generalized tonic-clonic status epilepticus within the 30 days prior to baseline while complying with appropriate AED therapy or an intermittent benzodiazepine use of more than four single administrations per month prior to baseline, a history (within the 6 months prior to baseline) of a psychiatric/mood disorder (DSM IV), not consistent with LGS, which required medical and/or electroconvulsive therapy were excluded.

Treatments
Patients must have been treated for at least 28 consecutive days immediately prior to randomization (Visit 1) with a fixed dose of one to three concomitant AEDs). All additional AEDs must have been discontinued at least 30 days prior to the 28-day baseline phase.

Following a baseline phase consisted of a 28 consecutive days (4 weeks) subjects were randomised to receive rufinamide or placebo. Randomization occurred on Day 0 and treatment began on the morning of Day 1. Rufinamide or matching placebo was administered orally with breakfast (approximately 7:00 - 8:00 a.m.) and again with supper or an evening snack (approximately 7:00 - 8:00 p.m.).

During the Titration Period, doses were increased based on weight. If tolerability problems arose, the dose may have been titrated more slowly at the investigator's discretion. However, the dose at the end of the Titration Period was to be the dose the patient remained on during the entire Maintenance Period. In case of poor tolerability during the Maintenance Period, dosage reductions were permitted.

Objectives
The objective of this study was to evaluate the safety and efficacy of rufinamide relative to placebo as adjunctive therapy in patients with inadequately controlled seizures associated with LGS.
Seizure frequency was expressed as the rate per 28 days in both the Baseline and Double-Blind Phases.

Outcomes/endpoints

Rufinamide would be considered effective if condition 1 and 2 were fulfilled (primary efficacy variables) :

1. The percent reduction in total seizure frequency per 28 days in the double-blind phase relative to the baseline phase was significantly greater ($p < 0.025$; two-sided) for rufinamide than placebo.

2. Both of the following end point were met:
• The percent reduction in tonic-atonic seizure frequency per 28 days in the double-blind phase relative to the baseline phase was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo.
• The seizure severity rating from the Global Evaluation of the patient's condition was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo.

Percent change in seizure frequency (PCH) was defined as PCH = 100*(T-B)/B, where T and B are the seizure frequency per 28 days in the double-blind phase and baseline phase, respectively. A negative PCH indicated a reduction in seizure frequency.
The seizure severity rating was a 7-point assessment performed by the parent/guardian at the end of the double-blind phase. A score of +3 indicated that the patient's seizure severity was very much improved, a score of 0 that the seizure severity was unchanged, and a score of –3 that the seizure severity was very much worse from baseline.