SCIENTIFIC DISCUSSION

1 Introduction

The Lennox-Gastaut syndrome (LGS) is a rare and one of the most severe forms of childhood epilepsy syndrome. The syndrome usually affects children between the ages of 1 and 8 years (typically between 3 and 5 years), but occasionally has its onset in children who are more than 8 years old. LGS begins in childhood but continues to manifest into adulthood in a large number of patients and has a significant morbidity and mortality. The hallmarks of the disease include the following triad:

- The presence of multiple seizure types: the most characteristic are tonic-atonic seizures and atypical absences, but tonic-clonic, myoclonic, and partial seizures are also frequently present. Tonic-atonic seizures often provoke sudden falls (commonly called drop attacks) and result in injuries.
- The presence of generalized discharges with slow spike-and-wave complexes in the electroencephalogram (EEG).
- The presence of mental retardation or a learning disability. In general, this is represented by a static encephalopathy, although the mental status may worsen in the course of the disease due to multiple causes, such as very frequent occurrence of seizures, sometimes subclinical, frequent head trauma from the falls associated with seizures (drop attacks), and undesirable cognitive effects of the high doses of antiepileptic drugs (AEDs) used to treat this very refractory type of epilepsy.

The aetiology of LGS remains unidentified in about half of the cases (cryptogenic LGS), whereas in others, the syndrome results from obvious brain injury (symptomatic LGS). The most common identifiable factor is a history of infantile spasms, occurring in up to one-third of the cases. Other causes include perinatal central nervous system trauma, meningitis and encephalitis, tumour, and severe head trauma. However, the electroclinical features are identical in cryptogenic and symptomatic LGS.
LGS accounts for approximately 1% of all new cases of epilepsy, although it may account for as many as 10% of the cases of severe epilepsy. Within European populations, the prevalence of LGS is 0.9 per 10,000 population across all age groups, and 0.7, 1 and 2 per 10,000 population in age groups between 0 and 19 years (EMEA/COMP Summary Report on an application for Orphan Medicinal Product Designation, COMP/390/03, 2004).

The long-term prognosis of LGS is frequently poor, with deteriorating mental function and persistently high rates of seizures. It is considered as an epileptic encephalopathy since epileptic phenomenon contributes to worsen the children condition. Seizure-free recovery is rare; fewer than 10% of patients became seizure-free in most reported series. Remission with preserved mentation occurs in very few patients; rather, IQ tends to deteriorate with age, and tonic seizures persist, but the slow spike-and-wave pattern does tend to resolve. Psychomotor delay and neuropsychiatric symptoms occur in 90% of LGS patients. Prolonged reaction time and information processing are the most impaired cognitive functions, which explains why these patients have a slow behaviour and are often rejected from school, even if intellectual capacity remains. Behavioural abnormalities occur in half the cases, including hyperactivity (most commonly), emotional instability, aggressiveness, destructive behaviour, autism, and antisocial personality. Such abnormalities and the arrest of educational progress are more prominent in older children and adolescents than in younger children. Chronic psychosis with episodes of acute exacerbation may also occur.
The mortality rate is difficult to assess: about 3% in the series of Gastaut, with a mean follow-up of 8 years and 7 months, and 7% in that of Loubier with a mean follow-up of 9 years and 9 months.

Current management of LGS is not satisfactory because the seizures associated with LGS are frequently unresponsive to standard anticonvulsants, in particular carbamazepine, phenytoin, and barbiturates. Valproate, often used as the drug of first choice, may help in controlling some seizure types, particularly atypical absence and myoclonic seizures. However, no controlled trials demonstrating its efficacy in LGS have been published. Benzodiazepines (clonazepam, clobazam, and

nitrazepam) are also frequently used as adjuvant intermittent treatment for LGS patients who have clusters of seizures. Nevertheless, no formal studies with these drugs have been reported. Newer AEDs, i.e., lamotrigine, felbamate and topiramate may be of benefit in patients with LGS. In one randomised clinical trial dedicated to LGS (adults and children mixed) for each of these compounds, the percentage change in tonic-atonic seizures or drop attacks with these AEDs has reportedly been about 25% greater than that seen with placebo A small number of patients became seizure free. In addition to their moderate efficacy, they are associated with potentially severe adverse reactions (aplasia and hepatitis with felbamate, skin rash with lamotrigine, cognitive disorders with topiramate).
Typically, either a benzodiazepine or one of the newer AEDs (lamotrigine, topiramate or felbamate) is used as add-on treatment, generally with valproate. Treatment with benzodiazepines, however, has sometimes been reported to worsen LGS and even to induce status epilepticus. The treatment of patients with LGS often involves polytherapy due to the lack of full response to any single AED. Even when a drug is initially effective, this may not persist long term. Nonetheless, patients usually benefit only minor improvements in seizure frequency and severity, as treatment success is uncommon in this condition.
Evaluation for a surgical approach (corpus callosotomy) is warranted in patients who are refractory to all these drug therapies. Surgery is purely palliative, however, and seldom produces total control of seizures.
Non-drug treatments for LGS, including ketogenic diet, vagal nerve stimulation for intractable drop attacks are used occasionally.

Rufinamide is a triazole derivative used as an antiepileptic drug (AED), structurally unrelated to currently marketed AEDs.

The primary *in vitro* pharmacodynamic data indicate that interacts with the inactivated state of the sodium channel and slows conversion to the active state thereby reducing the frequency of sodium-dependent action potentials in rat neurons, an effect that could contribute to blocking the spread of seizure activity from an epileptogenic focus.
Evidence from *in vivo* studies using animal seizure models showed that rufinamide is active in a broad range of animal models of epilepsy. No tolerance was observed in animals after repeated dosing.

Ciba-Geigy in Europe initiated the earliest clinical studies with rufinamide in 1987. Novartis, (merging of Ciba-Geigy and Sandoz), continued the development until 2001. Eisai Company, Limited. acquired the worldwide development rights to rufinamide from Novartis on 6 February 2004 for the submitted indication and further development work since this date has been carried out by Eisai.

Rufinamide was designated as Orphan in this indication by the Committee on Orphan Medicinal Products (COMP) (EMEA/OD/047/04) on 9th September 2004, adopted by the European Commission on 20th October 2004 (EU/3/04/240). It was designated as an Orphan on the basis that although satisfactory methods of treatment of LGS have been authorized in the Community, justifications have been provided to the COMP that rufinamide may be of significant benefit to those affected by the condition.
No protocol assistance in this indication was requested by the applicant.

2 Quality aspects

Introduction
Inovelon is presented as film-coated tablets containing 100, 200 or 400 mg rufinamide. The tablets are pink, 'ovaloid' in shape, slightly convex, scored on both sides. Each strength is identified by an embossed marking "Є 261", "Є 262" and "Є 263" only on one side of the tablet, for the 100, 200, and 400 mg strength, respectively.
Inovelon tablets are packaged in push-through PA/AL/PVC blister pack, also referred to as Alu/Alu blister pack in pack sizes of 10, 30, 50, 60 100 film-coated tablets for all strengths, whereas for the 400 mg strength only, an additional pack size of 200 tablets also exists.

Active Substance

Rufinamide, a triazole derivative, is the INN name of the active substance 1-(2, 6-difluoro-phenyl) methyl-1*H*-1, 2, 3-triazole-4-carboxamide. The molecular formula is $C_{10}H_8F_2N_4O$ and the Relative Molecular Mass 238.2. It appears as a fine, white, odourless and slightly bitter, not hygroscopic powder of needle shaped crystals with aggregates. It is practically insoluble in water, slightly soluble in methanol and very slightly soluble in ethanol. Due to the needle shaped crystals, the drug substance has a low bulk density, poor flow properties and strong tendency to agglomerate. The partition coefficient, log $P_{o/w}$ is 0.65, and the melting range is between 233°C and 238°C. There are four known polymorphic forms, A, A′, B and C; A being the thermodynamically stable form.

- Manufacture

The synthesis of the rufinamide drug substance is a 7-stage process. For an individual step, several batches may be combined for workup. If a batch of an intermediate or the drug substance fails to meet specifications, the material may be reworked according to the procedure described in the synthetic description, starting at an appropriate stage. The product is isolated and purified by several steps of re-crystallisation initially with 2-propanol and later with methanol.
The manufacturing process of rufinamide is adequately controlled by the testing of the intermediates.
Rufinamide manufactured by the current process is exclusively modification A, which is the thermodynamically stable form. All batches of drug substance used for technical, toxicological and clinical investigations show modification A. There is no evidence of hydrate formation from differential scanning calorimetry (DSC) or from the stoichiometry of the molecule.
Batch analysis data from nine batches were presented and the consistency of the results confirm that the active substance can be manufactured reproducibly as all results are well within limits.

- Specification

The specification for control of the drug substance includes tests for appearance, bulk density (USP), crystal modification (X-ray diffraction), identification (IR, HPLC), clarity (Ph. Eur.) and absorbance (UV) of 0.1 % MeOH solution, heavy metals, sulphated ash (Ph. Eur.), assay (HPLC), related substances (HPLC) and residual solvents (GC). In addition to this control imposed by the manufacturer, Eisai performs a test for particle size distribution and bulk density, keeping in mind the very low solubility and poor flowability of rufinamide.
Additional tests for residual solvents (GC, CE) and loss on drying (Ph. Eur.) are included in the specification for rufinamide batches that are reworked.
Batches analysis provided, including batches used in pre-clinical and clinical studies, confirm the suitability of the specifications.

- Stability

Since the original development was dane by Ciba/Geigy/Novartis, stability studies have been performed by both Novartis and Eisai.
Novartis has performed long-term, accelerated and photo stability tests, stress testing and forced decomposition studies under different conditions. Results from these Novartis studies were presented for three batches as primary data. This data package contains results from long term testing, at 25°C/60 %RH and 30°C/70 %RH for up to 3 years. For accelerated testing, 40°C/75 %RH, results were presented for up to 6 months. The drug substance has additionally been subjected to photostability testing in accordance with ICH Q1B Guideline and has been found not to be photolabile. The drug substance was subjected to extremes of temperature (50°C to 100°C) and found to be stable.

Eisai has also performed stability studies on four commercial size batches of rufinamide. These batches have been put in on-going stability and results for up to 6 months were presented, demonstrating no significant change in any tested parameter after storage at 25°C/60 %RH, 30°C/70 %RH or 40°C/75 %RH.

In conclusion, the results from the stability studies performed so far demonstrate that rufinamide is a stable and non-hygroscopic substance. Therefore, the applicant's re-test period proposal is justified when the bulk drug substance stored in the proposed packaging material and conditions.

Medicinal Product

- Pharmaceutical Development

At the very early stages of development, uncoated tablets of 1 and 10 mg were produced by direct compression. However, as the dose had to be increased, direct compression was impossible due to the poor flow characteristics of rufinamide. Higher strength (50 and 100 mg) uncoated tablets were developed using the dry "roller" compaction method, but flowability problems were observed during the dry compaction process. As a further increase of the dosage strength to 400 mg was necessary, further changes in the composition and in the manufacturing process of the product were made in order to achieve an acceptable weight and size of the 400 mg tablets and to overcome the technical problems observed in the roller compaction process. A wet granulation method was introduced together with formulation modifications pertaining to partial replacement of water insoluble excipients with water-soluble ones, as well as the employment of stronger disintegrant. In order to improve the wettability and to decrease the broad variability of the bulk density of the drug substance, a pre-densification step was introduced before granulation: the voluminous drug mass is wetted by a solution of sodium laurilsulfate in a high shear mixer. The active substance bulk density specification was set based on results from a bioequivalence study, comparing tablets manufactured with rufinamide of different bulk density. In addition, a particle size specification is proposed to control the quality of the active substance. Other bioequivalence studies were performed between the "roller compaction" formulation and the final formulation (wet granulation with predensification). The final formulation gave 20% higher AUC in bioavailability compared with the "roller compaction" tablets under fed conditions. However, there is no concern from this difference because only the final formulation has been used in the pivotal clinical study.
Apart from the processability problem, another difficulty has been the very low aqueous solubility of the active substance. Therefore, a flow through method was developed to control the dissolution rate of the tablets. Although dissolution times are long this does not present a problem since there is no permeability barrier.
A maximum storage period for the granules was determined to two months. It was further demonstrated that no change of polymorphism occurs during the manufacturing process.
Finally, a hypromellose film coat was introduced to mask the bitter taste of the drug substance. The tablet shape was also changed from round and flat to oblong cores and provision of scores as break-marks.
The tabletting mixture used for the 100, 200 and 400 mg formulations is the same and the different strengths are obtained by increasing proportionally the core weights to avoid different drug release characteristics and to facilitate production.
The excipients are commonly used in pharmaceutical products and were tested for compatibility. All the excipients meet the specifications defined in the current Ph.Eur. monographs or acceptable in-house standards. Purified water is the only solvent used for formulation processes including granulation and coating.

- Adventitious Agents

The magnesium stearate used in the production has been confirmed by the applicant and by the manufacturer to be of vegetable origin and is therefore not considered as a risk regarding BSE.
A certificate from the supplier of the lactose has been provided stating that "the lactose is manufactured from food grade cow's milk, sourced from healthy animals in the same conditions as milk collected for human consumption" fulfilling the NfG CPMP/BWP/1230/98 rev 1, which is satisfactory.

- Manufacture of the Product

Inovelon 100, 200 and 400 mg film-coated tablets are manufactured by standard wet granulation, tabletting and film-coating processes. A common granulate is used for all the three strengths. Granulation and pre-densification are performed on two equal sub-batches. The external phase excipients is added to the combined two sub-batches of granulates, then the mixture is sieved and lubrication is performed in a diffusion mixer.
The manufacturing process involves the following steps: pre-densification, mixing/kneading, wet granulation, drying, sieving/lubrication, compression and film-coating.
Following manufacture, the tablets are packed in bulk into an aluminium laminate bag for transport to the site of packaging into commercial packs.

- Product Specification

The specification for Inovelon film-coated tablets includes tests for appearance (visual), identification (TLC, HPLC), dissolution (Ph.Eur. -Apparatus 4/ HPLC), related substances (HPLC), assay (HPLC), and content uniformity (Ph.Eur.). Additionally, microbiological tests (Ph. Eur) are performed on one batch per year.
The tests and limits of the specifications Inovelon film-coated tablets are appropriate to control the quality of the finished product for the intended purpose.

- Stability of the Product

Eisai has performed stability studies on eight batches of tablets into commercial packaging for twelve months. Results from supporting stability studies performed on drug product stored in HDPE bottles were also presented. Additional stability studies have also been performed on Inovelon tablets in bulk pack. The applicant has committed that the on-going stability studies will continue for three years. The analytical methods used during the stability studies were the same as those applied for control of the drug product.
Stability studies results from twelve batches of all three strengths of Inovelon tablets manufactured by Novartis were presented as supportive data. Eight of those batches were packaged in the intended market packaging material for up to 36 months. Additional stability studies have also been performed on Inovelon tablets packed in HDPE bottles for up to 36 months and in bulk pack for up to 18 months.
Photostability studies have also been carried out on nine batches of tablets of all strengths.
The analytical methods used during the stability studies were the same as those applied for control of the drug product. Additional tests in the shelf-life specification were loss on drying, hardness and disintegration. All results from stressed, accelerated and long-term conditions were well within the specifications limits.

Based upon the on-going stability data from Eisai and stability data from Novartis, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Inovelon film-coated tablets is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3 Non-clinical aspects

The pivotal safety pharmacology studies investigating central nervous system (CNS), cardiovascular system (CVS) (including hERG assay), respiratory and renal function were performed in accordance with Good Laboratory Practice (GLP) regulations.
Most studies and all pivotal studies have been conducted in accordance with GLP, including toxicokinetic analysis.

Pharmacology
The CPMP Note for Guidance (NfG) on treatment of epileptic disorders (CPMP/EWP/566/98 rev1) addresses also non-clinical aspects for a medicinal product to be used for treatment of seizure disorders. "The neurobiological mode of action may be important since it may indicate in which seizure types and epileptic syndrome the drug may by efficacious." Further, "the study of the efficacy profile should be done in several experimental models, including models of generalised epilepsies with absences. It is important to know if the drug in development displays anti-seizure activity only or if it has a potential for antiepileptogenesis as well."

- Primary pharmacodynamics

In vitro studies
Rufinamide *in vitro* (at 1 μM ≈100μmol/L or higher) prolonged the recovery from sustained inactivation of Na^+ channels in cultured cortical neurons investigated with patch clamp technique indicating that rufinamide interacts mainly with the inactivated state of sodium channels and slows conversion to the active state, thereby reducing the frequency of action potentials. No significant inhibition at voltage-gated Na^+, K^+ or Ca^+ channels was observed.
In another experiment, rufinamide dose-dependently decreased the sustained repetitive firing with an IC_{50} of 3.8 μmol/l. The duration of action potential firing also decreased indicating an effect of rufinamide on firing of sodium-dependent action potentials that could contribute to blocking the spread of seizure activity from an epileptogenic focus. No extrapolation between *in vitro* concentrations of rufinamide and the *in vivo* situation in human will be performed since it is considered of limited value.
Rufinamide did not significantly interact with a number of neurotransmitter systems, including GABA, benzodiazepine, monoaminergic and cholinergic binding sites, N-methyl-D-aspartate (NMDA) and other excitatory amino acid binding sites. A weak interaction at β-adrenergic receptor sites was noted at a fairly high concentration.

In vivo studies
The *anticonvulsant activity* of rufinamide was investigated in a large number of relevant animal models of seizure disorders, mimicking generalised tonic-clonic, simple and complex partial seizures. No specific animal model exists for the Lennox-Gastaut syndrome.

In test of generalised tonic-clonic seizures such as the maximal electroshock test (MES test; mice/rats) or on seizures induced by pentylenetetrazol (mice), rufinamide dose-dependently suppressed seizures. In mice an ED_{50} of 19.2 mg/kg was determined using the MES test, and in rats the corresponding ED_{50} is 4-11 mg/kg following oral administration. When extrapolated to pharmacokinetic/toxicokinetic data, these effects were observed at or slightly below clinical exposure. No adverse effects were noted up to 45 mg/kg.
Rufinamide was active also in chemically induced seizures (pentylenetrazole and picrotoxin) in mice at higher ED_{50}´s compared to the MES test, but was without effect in picrotoxin induced seizures. The pharmacological profile is expected to be similar to carbamazepine rather than sodium valproate. The efficacy of rufinamide in the MES test was investigated after different pre-treatment times, varying between 1 and 8 hours. The largest effect was seen after short pre-treatment times, which correlates with the pharmacokinetic profile of rufinamide. When comparing protective indexes for several antiepileptic drugs, rufinamide was equally effective or more effective than conventional antiepileptics.

In animal models of epileptogenesis for partial seizures in cats using penicillin as a focal epileptogen, an inhibition of hippocampal and cortical after-discharges was observed after treatment with rufinamide 300 mg/kg. A reduction of seizures was also observed in chronically epileptic rhesus monkeys with recurring partial seizures after treatment with rufinamide 30-50 mg/kg daily for 15 days.

Evidence from *in vivo* studies using animal seizure models suggests that rufinamide is a long-acting drug.

To assess the effects of rufinamide on learning and memory, the electroshock-induced amnesia test and the step-down passive avoidance test were performed in mice. A reduction in electroshock-induced amnesia and an improvement in learning were observed in each test, respectively.
The analgesic potential of rufinamide was weakly effective in rat and guinea pig models of neuropathic pain (NP). In these models, its overall profile was equal to that of carbamazepine (CBZ), whereas lamotrigine (LTG) was somewhat more efficacious.

- Secondary pharmacodynamics and Safety pharmacology programme

Rufinamide did not produce any unexpected or toxic effects in the safety pharmacology studies, which were conducted in accordance with ICH S7A (CPMP/ICH/539/00).
The main CNS-related effects of rufinamide are slight CNS depressant action in both mice (100-300 mg/kg p.o.) and monkeys (200 mg/kg p.o.) in behavioural tests. In accordance with the proposed mechanism of action the CNS depressant effect is expected.
No effect on motor coordination, body temperature or hexobarbiton induced sleeping time was observed. Further, data on behaviour are also available from primary pharmacodynamic studies indicating few adverse effects except ataxia at high doses. In animal models of learning performance, improved learning was noted in mice at doses of 0.3-30 mg/kg p.o. The clinical relevance of this finding is unclear.

Rufinamide induced no or very slight cardiovascular effects in dogs (up to 10 mg/kg i.v.). No effect on blood pressure, blood flow, P-wave amplitude, P-Q interval, QRS interval and Q-T interval was observed. A slight decrease in heart rate was noted at the low and high dose level. Confirmation of lack of cardiovascular and ECG effects comes from long-term studies in dogs and Cynomolgus monkeys, at exposure level in the clinical range. Rufinamide had no effect on hERG current when investigated in human embryonic kidney cells at concentrations up to 1μM.

Only slight effects on respiratory system, renal system and blood glucose were observed, considered to be of low clinical relevance.

- Pharmacodynamic drug interactions

The ability of rufinamide to interact pharmacodynamically with other antiepileptic drugs was investigated using the MES test. The anticonvulsant effect of rufinamide was additive to that of other antiepileptic drugs. No pharmacodynamic interactions could be observed. Five days repeated treatment with rufinamide induced no tolerance in the MES test, while tolerance developed for diazepam and carbamazepine.

No anticonvulsant activity was observed with any of the rufinamide metabolites CGP 47291, CGP 47292 CGP 47293, CGP 47294 extracted from rat urine.

Pharmacokinetics

The analytical method to determine rufinamide in human plasma was shown to be applicable to dog, rabbit, rat and monkey plasma. Although validation and assays of the toxicology studies samples do not fit to the modern criteria, they were in accordance to the best practice at the time where the studies have been done.

Absorption
Rufinamide was slowly absorbed in all investigated species (mouse, rat, dog, Cynomolgus monkey and baboon), in addition, relatively slow clearance, and little or no first pass metabolism were observed. Non-linear absorption was observed at high doses with decreasing absorption with increasing dose, most markedly in dogs and Cynomolgus monkeys. The low absorption in dogs and baboons could have been caused by the solid dosage form used (crystalline substance in gelatine capsule) whereas for mice, rats and Cynomolgus monkeys, in which absorption was good, a liquid suspension was administered. There were no pronounced gender differences in systemic exposure.

The absorption of rufinamide was characterized by a low rate, with variable extent of absorption which was species-dependant. The absorption capacity for rufinamide was assessed in Caco-2 cells, and the predicted oral absorption was in the order of 80-90%.

Distribution
The distribution was similar in mice and in rats. The highest levels of radioactivity were found in liver (mouse, rat), adrenals (rat) and aorta (mouse). No specific affinity/uptake to organs/tissue was detected and no notable accumulation was observed after repeated dosing. Rufinamide rapidly and reversibly crosses the blood-brain barrier. Rufinamide also crosses the placenta and passes into fetal tissues in rats and rabbits, and was detected also in mammary glands. The serum protein binding was low (23-29%) in rat, dog, baboon and marmoset and comparable to that in man (34%).

Serum protein binding of rufinamide in species was low (23~35%). Radioactivity from labelled rufinamide was distributed throughout the body in rats, and there was no evidence of a peculiar or persistent affinity to specific organs and tissues. A marked and reversible transfer of rufinamide and/or metabolites to the embryo/fetal compartment was observed in rats and rabbits. Radiolabel was distinctly taken up into the mammary glands indicating the compound and/or metabolites could be excreted with the milk.

Metabolism
Biotransformation has been examined in rodents, dogs and primates and the metabolic pathways found include those present in humans. Systemic exposure to metabolites was low. Judging from urinary excretion data, the compound was cleared mainly by metabolism in all species tested and excretion of the products was divided between urine and faeces. Very little unchanged rufinamide was excreted into urine. The main metabolite was the carboxylic acid, designated CGP 47 292, formed by hydrolysis of the carboxylamide group, catalysed by carboxyesterase(s). Oxidative metabolism yielding CGP 47 291 was minor and apparently more pronounced in rodents than in dogs or primates. Rufinamide weakly induced drug-metabolizing enzymes in rat and mouse liver in a qualitatively similar manner to carbamazepine or phenobarbital. Rufinamide showed no significant capacity to inhibit the activity of the human P450 enzymes of relevance to drug metabolism. It can be concluded that the species used in the toxicity studies form the main metabolites in humans (CGP 47 292 and traces of CGP 47 291), and hence, have been exposed to these metabolites.

The choleliths (consisting of metabolite IV) seen in Cynomolgus monkey gall bladder in the repeated-dose studies and the fluoride-linked osteomas in mice observed in the carcinogenicity study, raised questions from the CHMP about their relevance to humans. ,
An additional metabolic pathway (to the metabolism by carboxylesterases) was proposed by the Applicant for the mouse and monkey, where rufinamide is metabolised through oxidation of the difluorophenyl ring, followed by fluoride substitution by glutathione and glutathione degradation via the mercapturic pathway, with subsequent formation of metabolite IV. Thorough investigations by the applicant have shown that glutathione-derived metabolites (including metabolite IV) could not be detected in humans. However, it cannot be completely excluded that small amounts of glutathione conjugates may be formed in humans. Therefore, the CHMP agreed that the effects seen after rufinamide exposure in mouse (osteomas and degeneration of submandibular glands) and Cynomolgus monkey (choleliths in gall bladder consisting of metabolite IV) can be considered as species specific.

Excretion
Excretion of rufinamide was rapid and complete in mice, rats, dogs, monkeys and baboons. Renal excretion was the predominant route of excretion in all species, except the baboon in which biliary excretion appeared to be significant.

Toxicology
All pivotal studies were conducted according to GLP standards.

- Single dose toxicity

Rufinamide is of low acute toxicity with approximate lethal oral doses of more than 5000 mg/kg in mice, 5000 mg/kg in rat and more than 2000 mg/kg in dogs. With intraperitoneal injection in rats the lethal dose was 1000 mg/kg. The clinical observations were mainly CNS related. No toxicokinetic data were available from the single toxicity studies. When comparing allometrically corrected non-lethal doses, the multiple to human maximum dose (48 mg/kg) was approximately 10 in the mouse and rat, and 20 in the dog.

- Repeat dose toxicity (with toxicokinetics)

Rufinamide was administered orally to mouse (3 months and 600 mg/kg/day), rat (up to 26/52 weeks and 600 mg/kg/day), Beagle dog (up to 26/52 weeks and 600 mg/kg/day), Cynomolgus monkey (12 months and 300 mg/kg/day) and wild-caught baboon (1 month and 300 mg/kg/day). The main target organ of toxicity was the liver in all species tested, and in rodents, the kidney.

In mice, up to 3 times increases in AST/ALT and ALP and hepatocellular hypertrophy (minimal to mild in males and minimal in females), single cell necrosis and/or hepatic pigment accumulation (in periportal areas, in Kupffer´s cells and hepatocytes) accompanied by increased relative and absolute liver weights at 200 and 600 mg/kg were seen. These effects occurred at an exposure level similar to the maximum clinical exposure (AUC). Although hepatocellular hypertrophy and increased liver weights are indicators of metabolic induction. rufinamide was only a weak inducer of drug-metabolising enzymes in male mice. The accumulation of unidentified pigment and increased ALT/AST and ALP is indicative of hepatic injury. Liver was also a target organ in the repeated-dose toxicity studies in rat and in the carcinogenicity studies in rat and mouse. The mechanism of these findings is not fully explained and the relevance for humans is uncertain. However, no significant liver toxicity were observed during the clinical trials.

Atrophy of the acinar epithelium of the submandibular salivary glands was characterised by a decreased number of secretory granules and increased amounts of pale, basophilic cytoplasm, occasionally vacuolated. These changes were of minimal severity, with the exception of one high dose female, which showed gland degeneration. The metabolic pathway in the mouse liberates fluoride ions (see pharmacokinetics) and a correlation between fluoride and the development of the submandibular glands has been discussed in the literature. As the fluoride liberating pathway is not relevant to humans, (see above section metabolism), the clinical relevance of the effects on the submandibular glands are not considered to be an issue for human safety.

In rats, mostly in male and to a much less extent in females, administration of rufinamide for 1 month and up to 52 weeks caused centrilobular hepatocellular hypertrophy and cytoplasmic vacuolation of cells of the anterior pituitary. These findings are related to increased T4 UDP-GT activity, seen after 8 days with a dose of 600 mg/kg. T4 UDP-GT enhances the clearance of thyroid hormones, which results in a reduction of negative feedback, activating TSH in the pituitary, and, in turn, activating the thyroid to produce thyroid hormones. Liver enzyme induction leading to disruption of the pituitary-thyroid axis is well known and species specific for the rat, and thus lacks relevance to human risk assessment. Hepatocyte enlargement and pigment accumulation in macrophages and Kupffer´s cells were seen at mid and high dose, even after 4 weeks recovery

In Beagle dogs, two moribund females were seen at mid and high doses in the 13-week study (87-6091) (another female at high dose had the same symptoms, but developed them later and could continue the study). The severe signs, clinical collapse, severe haematology and bone marrow changes, could be attributed, according to the applicant, to an auto-immune reaction.

Further, at doses of 600 mg/kg, hepatic effects included periacinar, intracanalicular or centrilobular intrahepatocellular bile accumulation, bile plugs and pigment deposits within hepatocytes or in bile canaliculi and focal perivascular inflammation with increased ALP, AST and ALT. Only partial reversibility was seen after 4 weeks in the 26/52 week study. The AUC for the 600 mg/kg dose was (mean female and male) 4430 µmol*hr/L, giving an exposure multiple to the maximum clinical exposure of approximately 2. Clinically, a 5 time increase of the above upper limit of normal was seen for bilirubin, AST and ALT in a few patients. Since the metabolic pathways in dogs and humans are similar, and metabolite CGF 47292 being a common major metabolite, the CHMP requested discussion on this finding. Investigations on the bile physiology in bile-duct cannulated dog that repeat-doses of rufinamide induced a change in bile composition and viscosity as well as an hypercholeresis. Although the mechanism of the cholestasis is not understood, the clinical experience overrules the question of the relevance to humans of these findings. In the dog, the NOAEL is set to 5 mg/kg (13-week study), where leukocytic infiltrates in the liver was seen in female dogs.

In non-human primates (Cynomolgus and baboon monkeys), the major findings were reversible liver weight increases, minimal transaminase increases, reversible hepatocellular hypertrophy and formation of choleliths in the gallbladder lumen. These choleliths were seen at necropsy in the 13-week study in both male and female monkeys in more than half of the mid-dose and in all monkeys in the high-dose, and in the 52-week toxicity study in 2 out of 7 monkeys at termination. In the 13-week study, these crystals were even seen in one high dose female after 4 weeks of recovery. No choleliths were found in the 1-month exploratory study in baboons. Analysis by HPLC with UV diode array detection, LC-MS and ^{1}H-NMR spectroscopy, revealed that the choleliths consisted of Metabolite IV, the insoluble 3-hydroxy-6-fluoro-2-S-cysteinyl conjugate of rufinamide. Metabolite IV is formed by fluoride substitution by glutathione and subsequent glutathione degradation via the mercapturic pathway. In the 52-week toxicity study, metabolite IV was present in urine and bile after 26 weeks of exposure to rufinamide, and at all dose levels, but absent after 4 weeks recovery. Metabolite IV has also been detected in rat and in dog bile. As explained above, as metabolite IV is not found in humans these findings are considered not to represent a risk for humans.
In the Cynomolgus monkeys, the NOAEL was set to 20 mg/kg, and in the baboon, the NOAEL was set to 30 mg/kg in the 1 month study. These exposures corresponds to approximately half the human exposure.

- Genotoxicity

Rufinamide has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations *in vitro* and *in vivo*. Additional tests of nucleus anomality and sister chromatid exchange have been conducted *in vivo* in Chinese hamsters. In all three *in vivo* tests, a maximum dose of 5000 mg/kg by oral gavage was used, and the animals are considered adequately exposed. No genotoxic potential was evident at concentrations up to the limit of toxicity or where signs of toxicity were observed.

- Carcinogenicity

104-week dietary carcinogenicity studies have been performed I the mouse and rat.
In mice, rufinamide was administered in the diet at doses of 0, 40, 120, or 400 mg/kg. Body weight gain reductions were-17% in males and -18% in females at 400 mg/kg. At 200 and 600 mg/kg, effects of rufinamide treatment were seen in the liver, bone and urinary system.

In the bone, hyperostosis was recorded, which is known to result from chronic, increased fluoride exposure. Treatment-related myelofibrosis was seen at mid and high dose in both females and males, even though no dose-response was seen for the females. The number of mice affected was 0, 1, 4, 10 and 3, 4, 10, 6 at 0, 40, 120 and 400 mg/kg, for males and females, respectively.

In the bone, osteomas were seen. Osteomas are benign and slowly growing neoplasms and most of them originate from the osteoblastic layer of the periosteum. Spontaneous osteomas appear at low frequency in most strains of mice, but these tumours can also be induced by mouse-specific polyomavirus and retrovirus. They are usually located to skull and larger bones of the limbs. In the cancer study in mouse, 0, 2, 3 and 9 mice with osteomas with periosteal origin were seen at 0, 40, 120 and 400 mg/kg, respectively. Multiple osteomas were observed in 7/14 osteoma-bearing mice and the most common locations of the osteomas were skull and pelvis. Thus, the osteomas displayed typical

characteristics of virus-induced osteomas. Additional electron microscopic analyses (included in the cancer study, but not conducted according to GLP) were performed on bone specimens from the mouse cancer study. Out of 11 examined samples, 5 did show occasional particles of appropriate size, but no evidence of budding or viral substructure. The remaining samples did show intracytoplasmic particles with c-type retroviral morphology, size and budding in association with osteoblasts, osteocytes and endothelial cells. The low incidence of osteomas in controls of contemporary studies, and no osteomas in the controls of the rufinamide cancer study makes it likely that the osteomas seen have mixed mechanistical origin, where both the presence of mouse-specific retroviruses and high levels of fluoride contribute to the development of osteomas. Neither of these contributors are relevant to human risk assessment, considering that no fluoride substitution takes place in the human metabolic pathway for rufinamide (see above). In the toxicokinetic study, the AUC is estimated to be 2400 µmol·hr/L at 400 mg/kg.

The changes in the urinary system consisted of minimal hydronephrosis, focal fibrosis in the kidney, dilation of the ureters and bladder affected mainly males in the high dose, likely due to high age.

In the liver, the same effects as in the pivotal repeated-dose toxicity studies were seen; increases in AST/ALT and ALP, liver hypertrophy and pigment accumulation in the macrophages (see above).
In addition, treatment-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in both sexes at 400 mg/kg. The mouse liver is known to be sensitive to tumourigenisis from agents causing microsomal enzyme induction, however, rufinamide was only a weak inducer of drug-metabolising enzymes in male mice. Comparison with historical controls for this strain shows that the incidence of liver tumour is within the range of the biological variability of the CD-1 strain of mice. No liver neoplasms were seen in the rat carcinogenicity study. Therefore this finding is not considered to be a concern for humans.

In rats, rufinamide was administered in the diet at doses of 0, 20, 60, or 200 mg/kg. Polyuria in both sexes at the high dose, and reduced body weight and food consumption were observed at all dose levels, with reductions in body weight gain of -30% in females and -13% in males at the high dose at termination. Plasma concentrations of rufinamide were detected in 6 out of 89 control samples, at approximately 4 times LoQ (0.05 µg/ml). This is not considered to invalidate the study.

In the liver at 60 and 200 mg/kg, centrilobular hepatocellular hypertrophy and megalocytosis was seen. It is agreed that centrilobular hepatocellular hypertrophy is related to enzymatic induction seen in rats. Megalocytosis might also be correlated with hepatocellular hypertrophy. However, megalocytosis occurred primarily in the females with 9/60 rats affected in the high dose, while 14/60 rats had centrilobular hypertrophy. In the males no cases of megalocytosis was seen in any dose group, but 16/60 and 36/60 rats were diagnosed with centrilobular hypertrophy in the mid and high dose, respectively. In addition, accumulation of pigmented hepatic macrophages and apoptosis, seen only in high dose females with 4/60 rats affected, were observed. As mention earlier (see repeat-dose toxicity), although the mechanism of liver findings is not fully understood, no significant signals of hepatoxicity have been identified in the clinical trials.

In the kidney, pelvic epithelial hyperplasia and pelvic mineralization was observed in both sexes at 60 and 200 mg/kg. Toxicity to the kidney (tubular dilation in the renal medulla and mineralization) at 60 mg/kg was seen in the dose-range finding study in juvenile rats (dosed up to day 35 post partum), and in the repeated-dose toxicity study 92-100. As kidney lesions were not found in longer repeat-dose toxicity studies and as these findings could be attributed in the carcinogenicity study to spontaneous lesions in aged rats (chronic progressive nephropathy), it was concluded that they were not considered of toxicological significance.
In addition, decreased bone marrow cellularity in males at 60 and 200 mg/kg, thymic atrophy in females at all doses and ovarian stromal hyperplasia at 60 and 200 mg/kg was seen. Ovarian stromal hyperplasia is likely related to old age. Since no effect was seen on the ovary in other toxicity studies, this is not considered to be a concern.

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 Choleliths	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.

The secondary efficacy variables were:

1) response to treatment (i.e., experiencing at least a 50% reduction in tonic-atonic seizure frequency during the double-blind phase relative to the baseline phase);
2) percent change in the frequency per 28 days for seizure subtypes other than tonic-atonic; and
3) the composite score for the Global Evaluation of the patient's condition.

Sample size

Approximately 128 patients were necessary to perform efficacy analyses in this study. This sample size was calculated based on the percent change in seizure frequency in the double-blind phase relative to the baseline phase.

No information was available on the performance of rufinamide in this population. It was assumed that rufinamide could deliver a percent reduction in seizure frequency 22.5% greater than that of placebo. Results from a similar trial with felbamate suggested a population standard deviation of no more than $\sigma = 35$.

Conditional on these assumptions and assuming a normal distribution, a two-sided t-test with a significance level of 0.025 has a statistical power of 91.3% to reject the null hypothesis of no treatment difference with approximately 64 randomized patients per treatment group. However, to guard against departures from normality, Wilcoxon rank-sum tests were used for this and the other two joint analyses of the primary efficacy variables.

Randomisation

Randomization was performed by the applicant using a validated system that automates the random assignment of treatment groups to randomisation numbers. Randomisation was in block of four at the country/centre level. The randomisation scheme was reviewed by the Company's trial statistician and was locked after approval.

Blinding (masking)

Study drugs were supplied as 100, 200, and 400 mg tablets with corresponding matching placebo tablets. The investigator, study site personnel and the Company's personnel involved in the monitoring or conduct of the study were blinded to the study drug codes. The codes were not available to the above personnel until the core study was completed and the final data review and database lock were performed, except in the case of an emergency.

Statistical methods

The data set used in all efficacy analyses was the intent-to-treat patient population, which consisted of all randomized patients who received double-blind study drug and provided seizure diary data during the double-blind phase. The data set used for all other analyses was the all-treated-patients population, which consisted of all patients who received at least one dose of study drug.

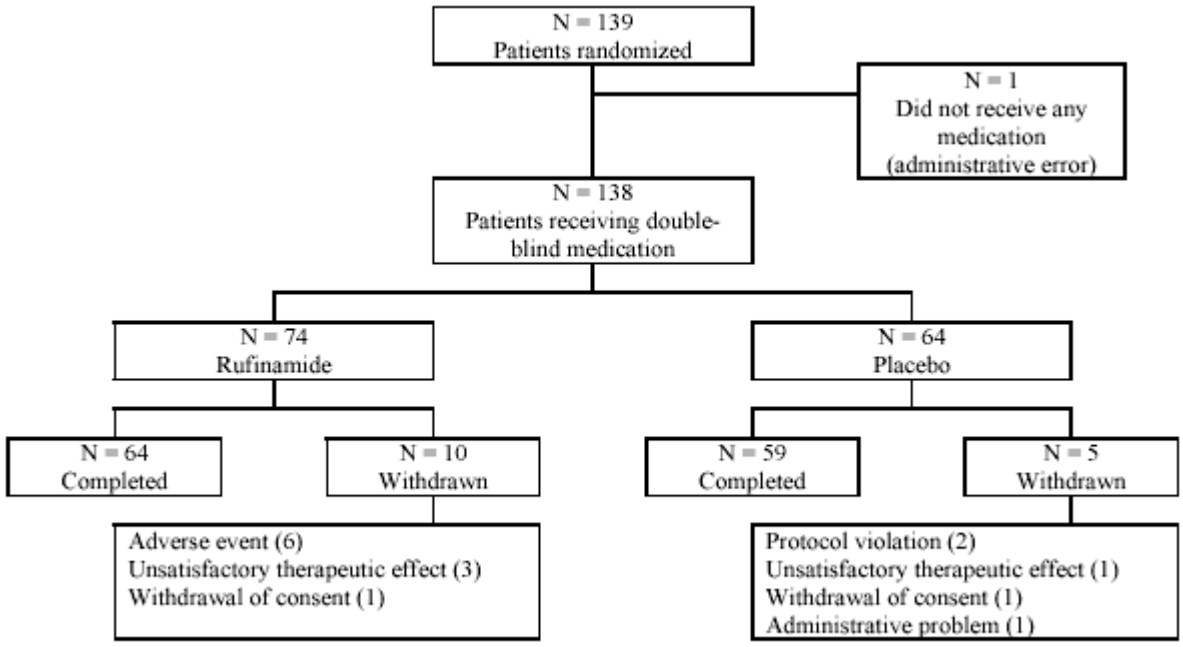
All tests performed by the Applicant to show statistical significance on the primary efficacy variables were two-tailed with a probability level of 0.025; a probability level of 0.05 was used to show statistical significance for the secondary efficacy variables.

A pooling scheme of countries was used for analyses that examined country effect due to the small enrolment at many centres and within countries, and the expected large variability in seizure frequency between patients. As a result, a factor "Region" consisting of three levels (USA, Brazil, Europe) was fitted in the analysis of response to treatment and in the exploratory analyses.

A data listing of the study-drug dosage administered to each patient during the Double-blind
Phase was provided by treatment group. The number and percent of patients exposed to study drug over distinct time intervals were calculated, and descriptive statistics were provided to summarize the duration of exposure to study drug by treatment group. In addition, descriptive statistics of the dose administered during the Maintenance Period (Visits 4 through 6) were provided. No interim analyses were planned.

RESULTS

Participant flow
The participant flow was the following:



Recruitment

A total of 43 centres in the following countries participated in the study: Belgium (2), Brazil (3), Germany (9), Hungary (3), Italy (3), Norway (1), Poland (2), Spain (2), and United States (18). Patients were enrolled in 36 of the centres.

Conduct of the study

Patient disposition for each treatment group

	Rufinamide		**Placebo**		**All treatments**	
	n	**%**	**n**	**%**	**n**	**%**
Number of patients randomized	75	100.0	64	100.0	139	100.0
Number of patients treated	74	98.7	64	100.0	138	99.3
Number of patients in intent-to-treat	74	98.7	64	100.0	138	99.3
Number for efficacy analysis						
primary variable 1	74	98.7	64	100.0	138	99.3
primary variable 2	73	97.3	60	93.8	133	95.7
primary variable 3	73	97.3	62	96.9	135	97.1
Number completed	64	85.3	59	92.2	123	88.5
Number discontinued						
- total	11[b]	14.7	5	7.8	16	11.5
- death	0	0.0	0	0.0	0	0.0
- for adverse events	6	8.0	0	0.0	6	4.3
- other[a]	5[b]	6.7	5	7.8	10	7.2

Primary variable 1 - percent reduction in total seizure frequency
Primary variable 2 - percent reduction in tonic-atonic seizure frequency
Primary variable 3 - seizure severity rating from the Global Evaluation of patient's condition
[a]Discontinued due to protocol violation, unsatisfactory therapeutic effect, withdrawal of consent, administrative problems
[b]Includes Patient USA/3054/2101 who was randomized but did not receive study drug.

There were no particular problems with the conduct of the study.
One randomized patient did not receive double-blind study drug due to an administrative error. The remaining 138 treated patients were included in the intent-to-treat population for percent change in total seizure frequency per 28 days (primary variable 1). One patient in the rufinamide group and four patients in the placebo group did not have any tonic-atonic seizures during the Baseline Phase and thus were excluded from the analyses for primary variable 2. One patient in the rufinamide group and two patients in the placebo group did not have an end-of-study seizure severity rating from the Global Evaluation of patient's condition and were thus excluded from the analyses for primary variable 3.
No patients were prematurely withdrawn from the study due to non-compliance.
Safety analyses were based on data from all 138 treated patients, including those who were excluded from the intent-to-treat populations for primary variables 2 and 3.
The study blind was not broken during the study for any treated patient. Thus, for all patients treated in this study, study blinding was preserved until all patients had completed the study, patient validity was determined, and the database was locked.

Baseline data

Demographic and baseline characteristics by treatment (All treated patients)

Characteristic	Rufinamide (N=74)		Placebo (N=64)		All treatments (N=138)	
	n	%	n	%	n	%
Sex						
Male	46	62.2	40	62.5	86	62.3
Female	28	37.8	24	37.5	52	37.7
Race						
White/Caucasian	62	83.8	53	82.8	115	83.3
Black	6	8.1	4	6.3	10	7.2
Other	6	8.1	7	10.9	13	9.4
Age (years)						
Mean (Range)	14.5 (4, 35)		13.6 (4, 37)		14.1 (4, 37)	
4 - <12	31	41.9	33	51.6	64	46.4
12 - <17	19	25.7	17	26.6	36	26.1
≥17	24	32.4	14	21.9	38	27.5
Weight (kgs)						
Mean (Range)	44.1 (15.5, 138.5)		40.2 (16.2, 86.0)		42.3 (15.5, 138.5)	
18 – 29.0	24	32.4	24	37.5	48	34.8
29.1 – 50.0	25	33.8	20	31.3	45	32.6
50.1 – 70.0	13	17.6	14	21.9	27	19.6
≥70.1	12	16.2	6	9.4	18	13.0

There were no notable differences between the two treatment groups with respect to sex, race, age, body weight.

Summary statistics of seizures in baseline phase (All treated patients)

	Rufinamide (N=74)			Placebo (N=64)		
	n	Median	Range	n	Median	Range
All types of seizures	74	290.0	48, 53760	64	205.0	21, 109714
Tonic-atonic seizures[a]	73	92.0	5, 14304	60	92.5	1, 13122
Atypical absence seizures	59	76.0	1, 2171	55	52.0	1, 4009
Tonic seizures	52	66.3	1, 14304	43	49.0	1, 1066
Atonic seizures	45	56.0	1, 4037	33	49.0	2, 13122
Myoclonic seizures	37	80.0	1, 38928	31	50.8	1, 92583
Tonic-clonic seizure	37	18.0	1, 336	27	15.0	1, 788
Unclassified	12	17.5	1, 202	13	16.0	1, 72
Partial seizures	11	49.0	1, 4195	9	41.0	3, 723
Absence seizures	8	31.0	1, 192	5	22.0	3, 84
Clonic seizures	7	36.0	1, 6021	1	51.0	

The median number of seizures of any type that occurred during the baseline phase was higher in the rufinamide group than in the placebo group due to median number for atypical absence, tonic, myoclonic, partial, and absence seizures higher in the rufinamide group. The median numbers of other types of seizures that occurred during the baseline phase were comparable in both groups.

The mean duration of LGS, defined as the time between diagnosis and baseline of the study, was 9.9 years for the rufinamide group and 9.6 years for the placebo group.

Summary of treatment exposure (All treated patients)

Cumulative exposure (units)	Rufinamide		Placebo	
	n	%	n	%
1 day	74	100.0	64	100.0
1 week	74	100.0	64	100.0
2 weeks	74	100.0	64	100.0
4 weeks	72	97.3	62	96.9
8 weeks	71	95.9	61	95.3
12 weeks	65	87.8	58	90.6
Summary Statistics (in days)				
Mean	79.2		81.0	
Median	84.0		84.0	
Range	(13, 112)		(13, 103)	

The target dosage was approximately 45 mg/kg/day of rufinamide (or placebo equivalent) or the maximum recommended daily dose in milligrams for the patient's weight, whichever was less.
In both treatment groups, more than 87% of patients received at least 12 weeks of treatment with the study drug. The median duration of exposure to study drug (84 days in both treatment groups) was consistent with the planned duration of the double-blind phase (84 days).

Summary of total number of concomitant AEDs used by patients in either treatment group (All treated patients)

Total Number of Concomitant AEDs	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
One	8	10.8	8	12.5
Two	38	51.4	35	54.7
Three	28	37.8	21	32.8

Valproate, lamotrigine, and topiramate were the most frequently used concomitant AEDs for both rufinamide- and placebo-treated patients during the study.

Summary of concomitant AEDs used by at least 10% of the patients in either treatment group during the double-blind phase (All treated patients)

Concomitant AED	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
Valproate	44	59.5	35	54.7
Lamotrigine	30	40.5	19	29.7
Topiramate	20	27.0	17	26.6
Clonazepam	14	18.9	7	10.9
Carbamazepine	12	16.2	12	18.8
Clobazam	10	13.5	8	12.5
Phenytoin	10	13.5	12	18.8
Phenobarbital	6	8.1	9	14.1

The types of concomitant AEDs used were generally comparable for the two treatment groups.

Outcomes and estimation
Primary efficacy results

The primary efficacy analysis showed statistically significant results in favour of rufinamide for all 3 primary variables ($p \leq 0.0041$), as shown below.

Primary efficacy variable 1: percentage change in total seizure frequency per 28 days
Primary efficacy variable 1 showed a significant difference between the 2 treatment groups in favour of rufinamide (p=0.0015). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency, as shown in the table below.

Summary of percent change in total seizure frequency per 28 days relative to baseline (ITT)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	74	290.0	(48.0, 53760.0)	64	205.0	(21.0, 109714.0)
Double-blind seizure frequency per 28 days	74	204.1	(5.4, 43262.3)	64	205.4	(50.7, 113165.0)
Percentage change in seizure frequency per 28 days from baseline[a]	74	-32.7	(-92.3, 381.4)	64	-11.7	(-82.8, 550.6)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0015

Cross-reference: Table 9-1 in the CSR for Study 022.

No significant treatment-by-region interaction was observed (p=0.7373). Rufinamide remained significantly superior to placebo after adjusting for the number of AEDs used at baseline (p=0.0021).

Primary efficacy variable 2: percentage change in tonic-atonic seizure frequency per 28 days
Primary efficacy variable 2 showed a significant difference between the 2 treatment groups in favour of rufinamide (p<0.0001). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 days, as shown in the following table:

Summary of percent change in tonic-atonic seizure frequency per 28 days relative to baseline (ITT patients)

	Rufinamide			Placebo		
	n[a]	Median	Range	n[a]	Median	Range
Baseline tonic-atonic seizure frequency per 28 days	73	92.0	(5.0, 14304)	60	92.5	(1.0, 13122)
Double-blind tonic-atonic seizure frequency per 28 days	73	60.7	(0.0, 12036.1)	60	76.2	(0, 17500)
Percentage change in tonic-atonic seizure frequency per 28 days from baseline[b]	73	-42.5	(-100, 1190.8)	60	1.4	(-100, 709.6)

[a] 5 patients (1 rufinamide, 4 placebo) did not experience tonic-atonic seizures during the Baseline Phase.
[b] Between-group comparison using Wilcoxon rank-sum test p-value < 0.0001.

Cross reference: Table 9-2 in the CSR for Study 022.

Primary efficacy variable 3: seizure severity subscale of Global Evaluation of patient's condition
Primary efficacy variable 3 showed a significant difference between the 2 treatment groups in favour of rufinamide (p=0.0041). An improvement in seizure severity was observed in 39 (53.4%) of the 73 rufinamide-treated patients compared to 19 (30.6%) of the 62 placebo-treated patients, as shown in the table below:

Summary of seizure severity rating of the Global evaluation of the patients' condition (ITT population)

	Rufinamide (N=73)		Placebo (N=62)	
Seizure severity	n[a]	%	n[a]	%
Very much worse	0	0.0	0	0.0
Much worse	3	4.1	4	6.5
Minimally worse	3	4.1	4	6.5
No change	28	38.4	35	56.5
Minimally improved	14	19.2	10	16.1
Much improved	16	21.9	8	12.9
Very much improved	9	12.3	1	1.6

Wilcoxon rank-sum test p-value = 0.0041

[a] 3 patients (1 rufinamide, 2 placebo) did not have a seizure severity evaluation.

Cross reference: Table 9-3 in the CSR for Study 022.

Secondary efficacy results

Response to treatment

The percent of patients who experienced at least a 50% reduction in tonic-atonic seizure frequency per 28 days, relative to baseline, was significantly higher in the rufinamide group (42.5%) than in the placebo group (16.7%) (p = 0.0020).

Summary statistics of patients who responded to treatment with at least a 50% reduction in tonic-atonic seizure frequency relative to baseline (Intent-to-treat patients)

	Rufinamide		Placebo			
Responder Rate	**n**	**%**	**n**	**%**	**Odds Ratio[a]**	**P-value[b]**
50%	31/73	42.5	10/60	16.7	3.81	0.0020

[a]The odds of a rufinamide-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days relative to the odds of a placebo-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days.

[b] p-value based on logistic regression model with treatment, region, sex, and age as explanatory variables.

Nevertheless, the percentage of seizure (tonic-atonic) free patients is low and not different in both arms (4.1% versus 3.3%). The median reduction in different isolated seizure type frequency is significant only for absences and atonic seizures.

In the composite score for the Global Evaluation of the patient's condition, the difference between the groups was not statistically significant (p = 0.3492).

Ancillary analyses

The applicant has performed additional exploratory analyses which do not indicate any association of age with the results of the primary efficacy analyses. Children, adolescents, and adult populations showed similar treatment effects. There was no association of age or weight at baseline with the results of the primary efficacy analyses. The number or type of concomitant AEDs a patient received was not associated with the results of the primary efficacy analyses. The efficacy of rufinamide could be observed when it was given in combination with commonly used AEDs in LGS, including valproate, lamotrigine, and topiramate. No evidence was found that rufinamide treatment caused an increase in the total seizure frequency, or that there was any development of short-term tolerance.

- Analysis performed across trials (pooled analyses and meta-analysis)

The patients within each age subgroup who received rufinamide had larger median decreases in seizure frequency than did the patients who received placebo. The only exceptions to this were noted in subgroups with very low numbers of patients.

The results for total seizure frequency, revealed that the median decreases became larger over the course of treatment and the persistence of the response in the rufinamide group but not in the placebo group. The large difference between rufinamide and placebo could be seen as early as Week 2.

In all cohorts, reduction in seizure frequency did not diminish over time, suggesting that at least a subpopulation of treated patients had seizure control maintained during long-term therapy. There appeared to be no development of tolerance to the anticonvulsant effect of rufinamide when cohorts with different lengths of drug exposure were analyzed.

In Study 022, the proportions of patients with increases in seizure frequency of 25% or less and with increases of more than 25% but less than 100% were lower in the rufinamide group than in the placebo group. The proportion of patients with 100% or greater increases in seizure frequency was small and no different between the 2 groups. In patients with primary generalized tonic-clonic seizures (Study 018), the proportion of patients with increases in seizure frequency was not different in the rufinamide-treated group compared to the placebo-treated group.

- Supportive studies

All the supportive placebo-controlled studies provide efficacy of rufinamide in patients with different types of epilepsy and of various age ranges.

1. Double-blind placebo-controlled adjunctive therapy studies in adults with partial seizures

Study AE/PT2

A multi-centre double-blind placebo-controlled randomized parallel group study.

The study was a 'proof of concept' study performed in a limited number of patients for duration of 4 weeks. The study included patients with primary generalised as well partial seizures. For the primary efficacy variable, seizure frequency ratio, and for response rate, there were trends for an improvement with rufinamide vs. placebo but no statistically significant differences. There was an unexpected worsening of seizure frequency in the placebo group for the (i) population.

The data used in the efficacy analyses are summarised below:

Median seizure frequency per 28 days in the Baseline and double-blind phases (All analysis populations in Study AE/PT2)

Data set[a]	Treatment	No. of patients	Median seizure frequency		Median % change relative to Baseline Phase
			Baseline Phase	Double-blind Phase	
(i)	Rufinamide	23	4.00	3.11	-41
	Placebo	21	6.46	8.30	+52
(ii)	Rufinamide	23	4.00	3.11	-41
	Placebo	19	8.62	9.33	+8
(iii)	Rufinamide	25	3.69	3.11	0[b]
	Placebo	25	4.62	5.19	0[b]

[a] Data set (i) included all patients who received treatment, except those who were seizure-free for the duration of both the Baseline and Double-blind Phases.
Data set (ii) included all patients who received treatment, except those who were seizure-free during the Baseline Phase.
Data set (iii) included all patients who received treatment (intent-to-treat population).

[b] Although the median seizure frequencies during the Baseline and Double-blind Phases differed, the median percentage change was 0% in both groups.

Study 021A

A multi-centre, double-blind, placebo-controlled, randomized, parallel-group study.

In this study, which included patients with inadequately controlled partial seizures that were being treated with 1 or 2 concomitant fixed-dose AEDs, the percentage reduction in total seizure frequency/28 days (primary variable) was significantly higher in the active group. However, no statistically significant difference was observed between the placebo and rufinamide groups with regard to partial seizure frequency per 28 days. The responder analysis demonstrated a significant difference for 50 and 25 % responder criteria in favour of rufinamide. Among patients who experienced secondarily generalized seizures during the baseline phase, there was no difference between the treatment groups in the percentage change in the frequency of this type of seizure during the double-blind phase.

The results of the primary efficacy variable: percentage change in total seizure frequency per 28 days are summarised in the table below:

Table 42. Summary of percentage change in partial seizure frequency per 28 days relative to baseline (ITT, Study 021A).

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	156	8.5	(3.0, 275.0)	156	8.0	(2.5, 578.5)
Double-blind seizure frequency per 28 days	156	7.6	(0.0, 552.2)	156	8.7	(0.0, 416.3)
Percentage change in seizure frequency per 28 days from baseline[a]	156	-20.4	(-100.0, 987.5)	156	1.6	(-100.0, 6837.8)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0158

Cross reference: Table 9-1 in the CSR for Study 021A.

Study 039

This was a multi-centre, double-blind randomised placebo-controlled parallel group monotherapy study in untreated patients 12 years of age or older with recent onset partial seizures. The study consisted of three phases: a 56-day baseline phase, a 56-day double-blind phase and an extension phase. Approximately 18 patients were planned but only 29 patients were randomised into the study, 14 to rufinamide and 15 to placebo. The study was terminated early due to the lack of enrolment. The number of enrolled patients was inadequate to obtain interpretable efficacy information, and no efficacy analysis was performed.

2. Double-blind, controlled studies of monotherapy and monotherapy substitution in patients with partial seizures

Study 038

Design: This was a multicentre, double-blind, placebo-controlled, randomized, parallel-group study of rufinamide as monotherapy in patients with refractory partial seizures who had completed an inpatient presurgical diagnostic examination. The study consisted of a 48-hour baseline phase and a 10-day double-blind treatment phase during which patients were randomized to receive either rufinamide or placebo. Patients who completed the study were allowed to enter an open-label Extension Phase.

Results: The median time to exit criteria (primary efficacy variable) was twice as along for rufinamide as for placebo, which was statistically significant. The results provide evidence for short-tem efficacy in monotherapy when the drug is tested in an extremely refractory population. However, the results may not be relevant for longer term clinical use.
The data are summarised in the table below:

Table 43. Summary statistic for time to seizure (ITT, Study 0389)

Study	Treatment	Time to	No. of events	Median (days)	(95% CI)	p-value
038	RUF 3200 mg/day	1st seizure	45	0.64	(0.50, 1.72)	0.0248[a]
	PLA		49	0.54	(0.19, 0.85)	
	RUF 3200 mg/day	2nd seizure	37	2.51	(0.98, 3.86)	0.0348[a]
	PLA		44	1.18	(0.80, 1.60)	
	RUF 3200 mg/day	3rd seizure	34	3.54	(2.60, 5.17)	0.0300[a]
	PLA		41	1.55	(1.26, 2.35)	
	RUF 3200 mg/day	4th seizure	30	4.39	(3.41, 7.64)	0.0509[a]
	PLA		34	2.37	(1.61, 3.67)	

[a] Based on Wald test from Prentice-Williams-Peterson proportional hazards regression model.

Cross reference: Appendix 5.1, Table 7 of the CSR for Study 038.

Study 016

A multicenter, double-blind, controlled, and randomized, parallel-group study.
The study compared the efficacy of treatment with rufinamide in monotherapy at a therapeutic dose with a subtherapeutic dose of rufinamide after gradual down titration of the baseline AED. No difference was observed for the primary efficacy variable percentage of patients meeting one of the exit criteria. For the secondary efficacy parameter median time to meeting one of the exit criteria, there was a trend for a better result with rufinamide 3200 mg/day but the difference was not statistically significant.

3. Double-blind placebo-controlled adjunctive therapy study in primary generalised epilepsy

Study 018

A multicenter, double-blind, placebo-controlled, randomized, parallel-group study.

In this study of primary generalised tonic-clonic seizures, there was a numerical trend for seizure reduction with rufinamide, but no statistically significant differences. This is consistent with the results in the pivotal study where no statistically significant effects were observed on primary generalised tonic-clonic seizures.

The primary efficacy variable data (percentage change in PGTC seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase) are shown in the table below:

Responder rates for Study 018.

Responder Rate	Rufinamide 800 mg/day n	%	Placebo n	%	Odds Ratio[a]	Confidence interval	p-value[b]
50%	30/74	40.5	24/74	32.4	1.44	0.72, 2.88	0.2966
75%	16/74	21.6	12/74	16.2	1.53	0.65, 3.59	0.3298
100%	4/74	5.4	7/74	9.5	0.57	0.16, 2.05	0.3871

[a] The odds of a rufinamide-treated patient experiencing a reduction in PGTC seizure frequency per 28 days from baseline relative to the odds of a placebo-treated patient experiencing a reduction in PGTC seizure frequency per 28 days relative to baseline.
[b] p-value based on logistic regression model.

4. Adjunctive therapy study in children with partial seizures

Study 021P

Design: A multicenter, double-blind, placebo-controlled, randomized, parallel-group study.

Results**:** This study failed to demonstrate any significant difference for the primary variable with rufinamide versus placebo in children and adolescents aged 4-16 years with inadequately controlled partial seizures. as shown in the table below.

Summary of percentage change in partial seizure frequency per 28 days relative to baseline (ITT, Study 021P)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	136	13.0	(3.0, 910.0)	131	14.5	(2.0, 243.0)
Double-blind seizure frequency per 28 days	136	11.7	(0.0, 1436.8)	131	14.0	(0.3, 307.7)
Percentage change in seizure frequency per 28 days from baseline[a]	136	-7.0	(-100.0, 758.1)	131	-12.8	(-97.2, 1293.0)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.6214

Cross reference: Table 9-1 in the CSR for Study 021P.

For 50 % responders, however, there was a strong trend for superiority with rufinamide. The target dose of rufinamide was the same as used in the pivotal study in LGS, 45 mg/kg and day.

A summary of these results is presented in the following table.

Response to treatment in Study 021P

	Rufinamide		Placebo		Odds Ratio[a]	
Responder Rate	n	%	n	%	(Wald CI)	p-value[b]
25%	56/136	41.2	48/131	36.6	1.25 (0.76, 2.06)	0.3796
50%	37/136	27.2	24/131	18.3	1.77 (0.98, 3.19)	0.0596
75%	18/136	13.2	12/131	9.2	1.56 (0.72, 3.40)	0.2619
100%	6/136	4.4	0/131	0.0	259[9] (---)	---

[a] The odds of a rufinamide-treated patient experiencing at least the given level of reduction in partial seizure frequency relative to the odds of a placebo-treated patient experiencing at least that level of reduction in partial seizure frequency.

[b] p-value based on logistic regression model with treatment, region, sex, and age as explanatory variables.

Cross reference: Table 9-4 in the CSR for Study 021P.

4. Open-label extension studies

Efficacy data were obtained during the open label extension phases of Studies 022, AE/ET1 and 021 A.

Study 022E

Design: a multicentre, open-label extension of study 022.

Inclusion criteria: Patients who had completed the 84- day Double-blind Phase of Study 022 were eligible to participate in the extension phase if the investigators thought they might benefit from treatment with rufinamide.

Treatment: The extension phase consisted of 2 periods: a double-blind conversion period and an open-label period. During the double-blind conversion period, patients who had received placebo in Study 022 began receiving rufinamide at a dose of approximately 10 mg/kg/day. The dose was titrated to approximately 45 mg/kg/day over a period of 14 days. Patients who had received rufinamide during Study 022 continued to receive the same dose of rufinamide during the double-blind conversion phase. The daily dose at the end of the conversion phase was used as the initial dose for open-label phase. During open-label treatment, the rufinamide dose could range from 10-45 mg/kg/day in 2 or 3 divided doses at the investigator's discretion. The newer FMI formulation of rufinamide was used in this study. The extension phase continued in a participating country until rufinamide was registered and launched in that country or until its development was terminated in that country.

Primary and secondary efficacy variables: The protocol did not define any efficacy variables for the extension phase, although the patients were required to record the occurrence of seizures in diaries. The following efficacy variables were identified by the Company after the study was completed:

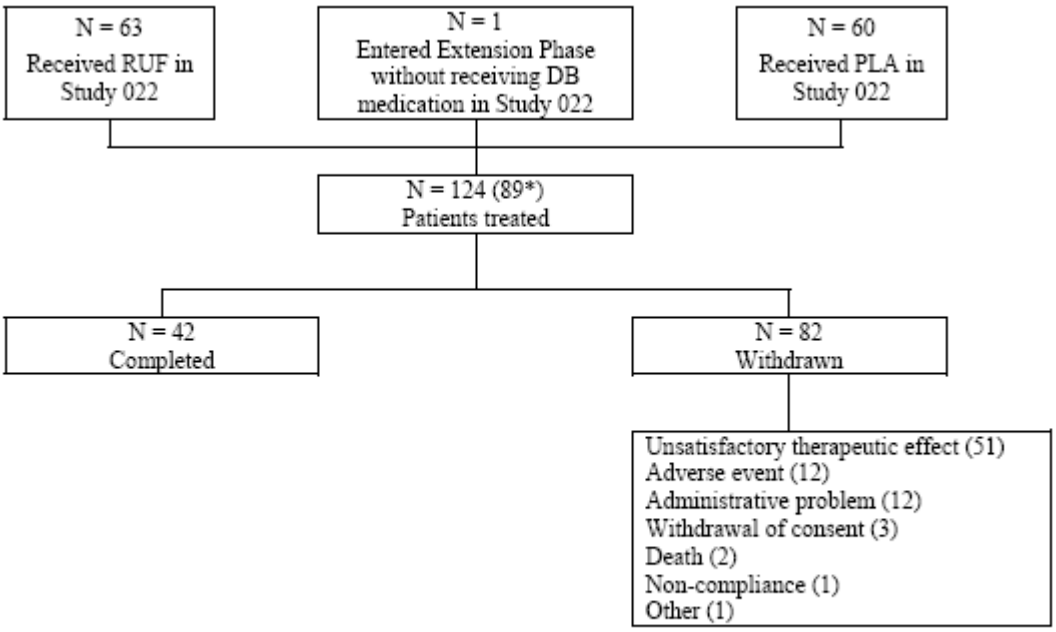
• Variable 1 - The percentage change in seizure frequency (total and tonic-atonic) per 28 days relative to baseline. This was determined for 2 cohorts: patients who had received rufinamide during both the double-blind phase (Study 022) and the extension phase (022E), and patients who had received placebo during the double-blind phase and rufinamide during the extension phase.

• Variable 2 - Response to treatment, defined as experiencing at least a 50% or 75% reduction in seizure frequency for the overall study period, the last 6 months, or the last 12 months of the study. This variable was determined for total seizure frequency and for tonic-atonic seizure frequency.

Tolerance to effectiveness was also evaluated using those 2 efficacy variables. If there were an initial percentage reduction in seizure frequency, followed by a lessening of the reduction or an increase in frequency, this would have suggested that patients were developing tolerance to the antiepileptic effect of rufinamide.

The disposition of the 124 patients treated in this study is illustrated in Figure 11.

Fig. 11. The disposition of the 124 patients treated in the extension study 022E



* Number of patients who were 16 years or younger.

Exposure to study drug in Study 022E

One patient was randomized to receive double-blind treatment in Study 022 but did not receive any study drug due to an administrative error. He was allowed to enter the Extension Phase directly. Of the remaining 123 patients, 63 had received rufinamide during the double-blind

Phase of Study 022 and 60 had received placebo. The median cumulative duration of exposure to rufinamide for patients who entered the Extension Phase was 432 days, with a range of 10 to 1149 days. Eighty-three (66.9%) of 124 patients received rufinamide for 1 year or more, 74 (59.7%) received rufinamide for 18 months or more, and 51 (41.1%) received rufinamide for 2 years or more. The median dose of rufinamide was approximately 1800 mg/day in the Open-label Period.

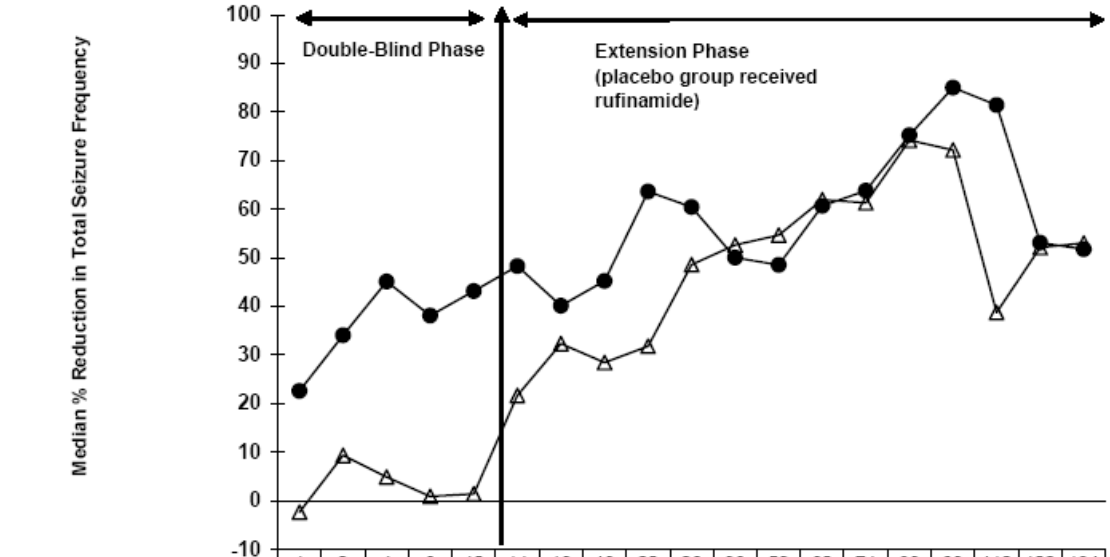
Results

Efficacy variable 1: Percentage change in seizure frequency per 28 days

Total seizures

Figure 12 illustrates the median percentage reduction from baseline in total seizure frequency for the rufinamide and placebo groups during the double-blind and extension phases.

Fig. 12. Median percentage reduction from baseline in total seizure frequency (Patients in Study 022E)



	1	2	4	8	12	14	16	18	22	26	38	50	62	74	86	98	110	122	134	(Week)
%Reduction-Placebo	-2.3	9.4	4.9	0.9	1.5	21.7	32.3	28.5	31.8	48.6	52.7	54.6	62.0	61.3	74.2	72.2	38.7	52.1	53.1	
%Reduction-Rufinamide	22.6	34.1	45.1	38.1	43.1	48.3	40.1	45.2	63.6	60.5	50.0	48.5	60.7	63.8	75.2	85.0	81.4	53.1	51.8	
Placebo (N)	60	60	60	59	59	59	56	54	51	48	45	40	35	26	21	19	14	10	6	
Rufinamide (N)	63	63	63	63	63	63	62	56	49	47	47	41	39	31	22	18	12	6	3	

Patients who received rufinamide in both phases demonstrated preserved reduction in total seizure frequency as the group continued from the double-blind phase into the extension phase. Patients who received placebo during the double-blind phase and then switched to rufinamide in the extension phase had a reduction in seizure frequency once they started receiving rufinamide. However, it should be noted that only 42 patients completed the study whereas 82 patients withdrew. As much as 51 patients withdrew due to insufficient therapeutic effect. It is therefore not possible to conclude whether there was tolerance development during the extension phase.

Efficacy variable 2: Response to treatment
Total seizures
The responder rates based on total seizure frequency are summarized in Table 47.

Table 47. Response to treatment based on total seizure frequency (Patients in Study 022E)

Responder Rate	Period	Responded/ Treated	% Response
50%	Overall	45/122	36.9
	Last 12 months	50/122	41.0
	Last 6 months	55/122	45.1
75%	Overall	26/122	21.3
	Last 12 months	29/122	23.8
	Last 6 months	34/122	27.9
100% (Seizure free)	Overall	0/122	0.0
	Last 12 months	0/122	0.0
	Last 6 months	2/122	1.6

Cross reference: Table 9-3 in the CSR for Study 022E.

Forty-five percent (45%) of the patients had at least a 50% reduction in total seizure frequency during the last 6 months of treatment. The percentage of patients with a 50% response during the last 12 months was 41.0%. The 50% response rate for total seizure was 36.9% overall. For at least a 75% reduction in total seizures, the response rates were lower but the pattern was similar. Two of 122 patients (1.6%) were seizure-free for the last 6 months of treatment.

In summary, the patients who switched from double-blind placebo to open-label rufinamide responded to treatment with decreases in seizure frequency. However, only 42 of 124 patients completed the study, whereas 82 withdrew and of these, 51 patients withdrew due to insufficient therapeutic effect. It is possible that a proportion of these 51 patients withdrew due to tolerance development with reduced efficacy. The results from the extension study do not answer the question whether there is development of tolerance to the anticonvulsant effect of rufinamide during long-term treatment.

Studies AE/ET1 E and 021AE

Efficacy date were obtained during the open-label phase of Studies AE/ET1 and 021A. Patients who had completed the double-blind phase of the studies were eligible to participate in the Extension Phase (395 patients were treated in study AE/ET1E and 240 in study 021AE).
The Extension Phase consisted of 2 periods: an open-label Conversion Period and an Open-label Period. During the Conversion Period, all patients received rufinamide according to a recommended titration schedule based on the dose of study drug (rufinamide or placebo) they had received during the double-blind phase. After completion of the Conversion Period, each patient entered the Open-label Period.

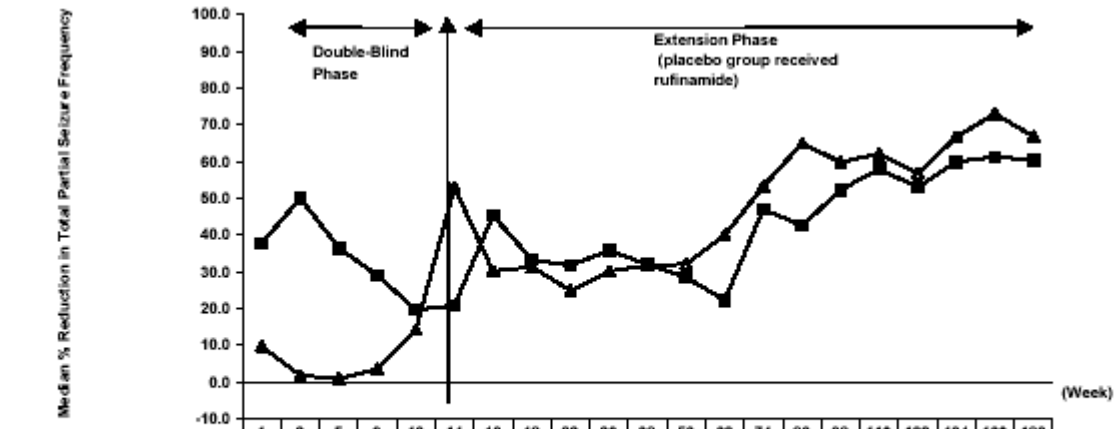
The following efficacy variables were identified after the study was completed:

• Variable 1 - The percentage change in partial seizure frequency per 28 days relative to the baseline phase. This was determined for 2 cohorts: patients who had received rufinamide during both the double-blind phase (Study 021A) and the Extension Phase (021AE), and patients who had received placebo during the double-blind phase and rufinamide during the Extension Phase.

• Variable 2 - Response to treatment, defined as experiencing at least a 50% or 75% reduction in seizure frequency for the overall study period, the last 6 months, or the last 12 months of the study. This variable was determined for total seizure frequency and for tonic-atonic seizure frequency.

The results were similar in the 2 extensions, so only study 021AE is presented.

Efficacy variable 1: Percentage change in seizure frequency per 28 days
Patients who received placebo during the core study and then switched to open-label rufinamide showed decreases in seizure frequency, which, over time, became similar to those experienced by patients who received both double-blind and open-label rufinamide.



	1	2	5	9	13	14	16	18	22	26	38	50	62	74	86	98	110	122	134	160	186
%Reduction-Placebo	9.7	1.8	0.9	3.6	14.3	52.9	30.2	31.4	24.9	30.2	31.7	32.1	40.0	53.3	65.1	59.8	62.1	56.8	66.7	73.1	66.8
%Reduction-Rufinamide	37.8	50.0	36.5	29.0	19.7	20.8	45.3	33.3	31.7	35.8	32.0	28.5	22.2	47.0	42.6	52.4	58.1	53.0	60.0	61.3	60.5
Placebo(N)	129	129	128	128	128	129	126	122	118	106	95	82	74	67	63	56	52	47	37	30	18
Rufinamide(N)	111	111	111	111	111	111	108	105	104	96	92	88	79	74	71	67	65	63	53	41	23

Efficacy variable 2: Response to treatment

Approximately 22% of the patients maintained at least a 50% reduction in total seizure frequency during treatment with rufinamide. The rate was approximately 29% for those who had at least a 50% reduction during the last 6 or 12 months of treatment. For at least a 75% reduction in total seizures, the response rates were lower but the pattern was similar. Five (2.1%) patients were seizure-free for the last 6 months of treatment.

Response to treatment based on partial seizure frequency

Responder Rate	Period	Responded/ Treated	% Response
50%	Overall	53/238	22.3
	Last 12 months	69/238	29.0
	Last 6 months	70/238	29.4
75%	Overall	18/238	7.6
	Last 12 months	35/238	14.7
	Last 6 months	42/238	17.6
100% (Seizure free)	Overall	2/238	0.8
	Last 12 months	4/238	1.7
	Last 6 months	5/238	2.1

In summary, approximately half of the 635 patients who participated in these studies received rufinamide for a cumulative duration of at least 2 years. The group of patients who had received rufinamide in the double-blind phase and entered the Extension Phase continued to show reductions in seizure frequency. The group of patients who switched from double-blind placebo to open-label rufinamide quickly responded with improvement in seizure frequency, which eventually matched that attained by rufinamide-treated patients. The median reduction in seizure frequency did not diminish over time in the open-label Extension Phase in patients who had received rufinamide or placebo during the double-blind phase.

- Discussion on clinical efficacy

There is a single pivotal clinical trial conducted in Lennox-Gastaut syndrome (study 022 and its extension 022E). Study 022 is a multicenter, randomised, double-blind, placebo-controlled, parallel study comparing the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome. The study design was in accordance with current standards to determine efficacy of antiepileptic drug and design is comparable to published study design supporting the approval of felbamate, topiramate and lamotrigine in this indication.

The diagnosis of LGS was based on the International League Against Epilepsy (ILAE) and confirmed with direct 6- to 24-hour video-EEG recordings.
The patient population, as chosen on the basis of the inclusion/exclusion criteria, was appropriate and representative of patients with LGS, due to the substantial proportion of children included in the present trial (more than 2/3).

The percent change in total seizure frequency per 28 days during the double-blind phase relative to the baseline phase (Primary efficacy variable 1), showed a significant difference between the two treatment groups in favour of rufinamide ($p = 0.0015$). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency.
The percent change in tonic-atonic seizure frequency per 28 days during the double-blind phase relative to the baseline phase, showed a significant difference between the two treatment groups in favour of rufinamide ($p < 0.0001$). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 days.
The seizure severity rating at the end of the double-blind phase, showed a significant difference between the two treatment groups in favour of rufinamide ($p = 0.0041$). An improvement in seizure severity was observed in 39 (53.4%) of the 73 rufinamide-treated patients compared to 19 (30.6%) of the 62 placebo-treated patients.

Nevertheless, there was a systematic strong baseline imbalance with respect to one of the two primary endpoints: i.e. the total seizure frequency at baseline. This strong imbalance also occurred for some seizure subtypes. The baseline total seizure frequency median was 290 in patients treated with rufinamide and only 205 in patients treated with placebo. Hence, patients treated with placebo were less severe at baseline than those treated with rufinamide. The medians estimated over the double-blind period were similar between the two treatments: i.e. 204.1and 205.4 in the rufinamide and placebo groups respectively. Thus, it cannot be excluded that the treatment effect might be explained entirely from this strong baseline imbalance.
At the request of the CHMP further analysis have been performed by the applicant.
Hodges-Lehmann estimators and 95% confidence intervals of the treatment effect for all seizure types using percent change from baseline in seizure frequency, change from baseline in seizure frequency, and post-baseline seizure frequency (including baseline seizure frequency as covariate) were performed. Unfortunately, as baseline unadjusted analysis are missing, it is not possible to exclude that results of primary efficacy variable 1 (the percent change in total seizure frequency per 28 days during the double-blind phase relative to the baseline phase) might be explained entirely from this strong baseline imbalance.
Nevertheless, primary efficacy variable 2 (the percent change in tonic/atonic seizure frequency per 28 days during the double-blind phase relative to the baseline phase) (where there was no imbalance observed at baseline) and primary efficacy variable 3 (the seizure severity rating at the end of the double-blind phase), showed a highly significant difference between the two treatment groups in favour of rufinamide on quantitative and responder analysis.
These results are consistent and robust as confirmed by the results obtained in the sensitivity analysis.

The PK-PD analysis showed that reduction in total seizure frequency, reduction in tonic-atonic seizure frequency, and improvement in seizure severity were related to the rufinamide serum concentration, i.e., higher exposure to rufinamide was related to seizure improvement.

Children, adolescents, and adult patients of either sex showed similar treatment effects.

The open-label study (study 022E) showed that the group of patients who switched from double-blind rufinamide to open-label rufinamide continued to respond to treatment with decreases in seizure frequency that were as large as, or larger, than the responses during double-blind treatment. The group of patients who switched from double-blind placebo to open-label rufinamide quickly responded to treatment with marked decreases in seizure frequency. As open-label treatment continued, these patients eventually attained levels of seizure reduction that were comparable to those in patients who had received both double-blind and open-label rufinamide.

A satisfactory maintenance of effect was seen at more than 18 months, without any obvious sign of tolerance. However long-term efficacy and absence of tolerance have not been demonstrated convincingly. A statement has been included in the SPC.

Rufinamide showed a moderate efficacy on partial seizures in adults and adolescents as adjunctive therapy (studies AE/PT2, AE/ET1 and 021A) and as monotherapy of substitution in adults and adolescents (studies 016 and 038), but not in children with refractory partial seizures (study 021P). In addition, there was no significant efficacy found on partial seizures in adults as monotherapy comparing high versus low doses, as well as in primary generalized epilepsy in adults and children over 4 years (study 018), and the effect on associated seizure types, absence and myoclonic seizures, was inferior to placebo. It is true that this population included was very small for these seizure types, and subject to high individual variations. Thus, study 018 failed to bring supportive notion of efficacy in generalized syndromes. No antiepileptic mechanism is known for rufinamide that could explain a better effect of rufinamide in LGS than in the major types of epilepsy. This was a concern for the external validity of efficacy.
Therefore, further information was requested by the CHMP including data about titration, maintenance dose, dose- response relationship, pharmacokinetics and short term safety in these supportive studies.
In the response by the applicant, overall the efficacy of rufinamide as an antiepileptic drug is supported by three positive trials in adults with partial seizures in which significant differences in seizure frequency were seen versus placebo. The trial in paediatric patients with partial seizures did not meet the primary efficacy endpoints. However, the responder rate approached significance (p=0.0596).
In patients with primary generalized seizures rufinamide efficacy has not been demonstrated. Nevertheless, relatively low rufinamide dose (800 mg/day) have been used. Thus these data give some reassurance for the external validity of the results.

Clinical safety

The population of all patients with epilepsy who have received at least 1 dose of rufinamide in a controlled or open-label clinical study or in an open-label extension includes a total of 1,978 patients. In addition to safety documentation for all patients with epilepsy, the applicant has submitted analyses of different subpopulations of patients who have been exposed to rufinamide. The different subpopulations for which safety data have been provided are listed below:

- Double-blind, adjunctive therapy study in LGS: This population includes all patients who received at least 1 dose of rufinamide or placebo in the pivotal study, Study 022 (N=74 rufinamide-treated patients and N=64 placebo-treated patients).

- Double-blind, adjunctive therapy study in LGS (with open-label extension): This population includes all patients who 1) received double-blind rufinamide in the pivotal study, Study 022, and did not enter the Extension Phase (Study 022E), 2) received double-blind rufinamide in Study 022, entered the Extension Phase, and received at least 1 dose of open-label rufinamide; and 3) received double-blind placebo in Study 022, entered the Extension phase, and received at least 1 dose of open-label rufinamide (N=135 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

- Double-blind studies in paediatric patients: This population includes all patients who received at least 1 dose of rufinamide or placebo and either were enrolled in double-blind Study 021P (paediatric patients only) or were ≤16 years old and enrolled in another double-blind study in epilepsy, including the LGS study (N=212 rufinamide-treated patients and N=197 placebo-treated patients).¨

- Double-blind, adjunctive therapy study in paediatric patients (with open-label extension): This population includes all patients in the preceding population who 1) received double-blind rufinamide only, 2) received double-blind rufinamide, entered an Extension Phase, and received at least 1 dose of open-label rufinamide; and 3) received double-blind placebo, entered an Extension

Phase, and received at least 1 dose of open-label rufinamide (N=391 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

- All treated patients with epilepsy (double-blind studies): This population includes all patients with epilepsy who received at least 1 dose of study drug in a double-blind clinical study (N=1,240 rufinamide-treated patients and N=635 placebo-treated patients).

- All treated patients with epilepsy: This population includes all patients with epilepsy who received at least 1 dose of rufinamide in a controlled or open-label clinical study or in an open-label extension (N=1,978 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

The number of patients in each analysis population, by study is summarised in the table below. The largest population, "All treated patients with epilepsy", included a total of 1,978 patients. In this assessment report, focus is on the two largest safety populations, "All treated patients with epilepsy (double-blind studies)" [n=1875] and "All treated patients with epilepsy" [n=1978].

Table. Number of patients in each analysis population, by study

	Number of patients										
	DB, adjunctive therapy study in LGS		DB, adjunctive therapy study in LGS (with OL extension)		DB studies in pediatric patients		DB studies in pediatric patients (with OL extensions)		All treated patients with epilepsy (double-blind studies)		All treated patients with epilepsy
Study	RUF	PLA	RUF	PLA	RUF	PLA	RUF	PLA	RUF	PLA	RUF
AE/ET1					8		8		514	133	514
AE/ET1E[a]											83[b]
AE/PT2									50[c]		50[c]
016									142		142
016E[a]											NA
018					14	11	14	11	78	75	78
018E[a]							10				64
021A					1		1		156	157	156
021AE[a]											129
021P					136	132	136	132	136	132	136
021PE[a]							119				119
022	74	64	74	64	50	50	50	50	74	64	74
022E[a]			61[b]				47				61[b]
027											16
027E[a]											NA
038					3	3	3	3	52	52	52
038E[a]							2				44
039						1		1	14	15	14
039E[a]							1				13
0101											209
2301											(73[d])
AE/PT1									15[e]	4	15
AE/PT3									9	3[f]	9
Total	74	64	135	64	212	197	391	197	1,240	635	1,978

[a] E indicates an open-label extension of a double-blind study. The number of patients shown in the rows for extension studies represent patients who received placebo during the double-blind study and rufinamide during the open-label study.

[b] Includes 1 patient who did not receive study drug in a double-blind study due to administrative problems and was allowed to enter the extension of the study directly.

[c] This was a double-blind, placebo-controlled study in which 25 patients received rufinamide and 25 patients received placebo for up to 4 weeks. In addition, the study included 2 pharmacokinetic evaluation periods in which all patients in both treatment groups received single doses of rufinamide 800 mg.

[d] These patients had received rufinamide in an open-label study that was terminated, and were allowed to continue receiving the drug in this compassionate-use study. These 73 patients are counted once in the total for this column.

[e] 12 patients with epilepsy and 3 healthy volunteers.

[f] These 3 patients also received a single-dose of rufinamide; they were included only in the placebo group.

The following table summarizes the demographic characteristics of all treated patients with epilepsy. Approximately half of the 1,978 patients exposed to rufinamide were males. The mean age was 31.3 years, and 77.6% of the patients were between the ages of 17 and 64 years. The mean weight was 66.8 kg, and 78.4% of the patients weighed more than 50 kg.

Table. Patient demographics for all treated patients with epilepsy (n=1,978).

	Rufinamide[a] (N=1,978)	
Characteristic	**n**	**(%)**
Sex		
Male	999	(50.5)
Female	979	(49.5)
Race[b]		
White/Caucasian	1,139	(57.6)
Black	86	(4.3)
Oriental	6	(0.3)
Other	100	(5.1)
Not reported[c]	647	(32.7)
Age, years		
Mean (Range)	31.3 (1-81)	
<12	234	(11.8)
≥12 – 16	183	(9.3)
≥17 – 64	1,534	(77.6)
≥65	27	(1.4)
Weight, kg		
Mean (Range)	66.8 (13.2-158.3)	
≤29	152	(7.7)
>29 – 50	275	(13.9)
>50	1,551	(78.4)

[a] Includes all patients who received rufinamide during open-label studies, double-blind studies, and extension studies, including patients who received placebo during a double-blind study and then received rufinamide during an extension study.

[b] The possible choices for race on the rufinamide CRFs that collected this information were white/Caucasian, black, oriental, or other.

[c] Information about race was not collected in all studies.

- Patient exposure

The extent of exposure to study drug for all rufinamide-treated patients with epilepsy is summarized by median daily dose in Table 50. Median doses were less than 1,600 mg/day for 939 (47.5%) patients, 1,600 to less than 2,400 mg/day for 381 (19.3%) patients, 2,400 to 3,200 mg/day for 598 (30.2%) patients, and more than 3,200 mg/day for 60 (3.0%) patients. The duration of exposure to these median daily doses ranged from less than 1 month to 4 years or more. More than half of the 939 patients with median doses of less than 1,600 mg/day were treated for at least 6 months. More than half of the 1,039 patients with median doses of 1,600 mg/day or more were treated for at least 12 months.

Table. Duration of exposure to rufinamide by median daily dose in mg/day
(All treated patients with epilepsy**)**

Cumulative Duration of Exposure[b,c]	Median dose[a] (mg/day) <400 (N=117) N	(%)	400 - <1,600 (N=822) N	(%)	1,600 - <2,400 (N=381) N	(%)	2,400 - ≤3,200 (N=598) N	(%)	>3,200 (N=60) N	(%)	All doses (N=1,978) N	(%)
0 - <1 month	117	(100)	822	(100)	381	(100)	598	(100)	60	(100)	1,978	(100)
1 - <3 months	104	(89)	751	(91)	361	(95)	562	(94)	60	(100)	1,838	(93)
3 - <6 months	75	(64)	571	(69)	293	(77)	516	(86)	58	(97)	1,513	(76)
6 - <12 months	41	(35)	467	(57)	227	(60)	451	(75)	53	(88)	1,239	(63)
12 - <24 months	11	(9)	316	(38)	173	(45)	376	(63)	46	(77)	922	(47)
24 - <36 months	1	(1)	125	(15)	86	(23)	206	(34)	27	(45)	445	(22)
36 - <48 months	0		54	(7)	43	(11)	92	(15)	14	(23)	203	(10)
≥48 months	0		23	(3)	12	(3)	31	(5)	1	(2)	67	(3)

[a] Median daily dose starting in the Maintenance Period. Dose calculations do not include titration information.
[b] 1 month = 30 days
[c] Includes patients with exposure to rufinamide during any open-label, double-blind, and/or extension phases.

- Adverse events

Events that were expected due to the trial indication (such as seizures in patients with epilepsy) were not treated as adverse events or serious adverse events, unless the event represented a significant worsening of the symptom (e.g., new seizure type, clinically significant increase in seizure severity, status epilepticus or hospitalization, etc.). The investigators were instructed to record adverse events using standard medical terminology. For the CSRs, the specific terms that the investigators recorded were coded to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. To maintain consistency in terminology for this safety summary, all investigator terms from all studies were recoded using MedDRA.

Adverse events data were pooled using the analysis populations defined in Section IV.1

An overview of all adverse events, deaths, serious adverse events, and adverse events leading to discontinuation of therapy is presented in the next table.

Table. Overview of adverse events, deaths, non-fatal serious adverse events, and adverse events leading to discontinuation of therapy

	Double-blind, adjunctive study in LGS		Double-blind studies in pediatric patients		Double-blind studies in patients with epilepsy		All treated patients with epilepsy
	RUF (N=74) N (%)	PLA (N=64) N (%)	RUF (N=212) N (%)	PLA (N=197) N (%)	RUF (N=1,240) N (%)	PLA (N=635) N (%)	RUF (N=1,978) N (%)
Any adverse event	60 (81.1)	52 (81.3)	177 (83.5)	147 (74.6)	975 (78.6)	497 (78.3)	1,761 (89.0)
Maximum severity							
Mild	17 (23.0)	31 (48.4)	65 (30.7)	82 (41.6)	394 (31.8)	240 (37.8)	466 (23.6)
Moderate	33 (44.6)	15 (23.4)	93 (43.9)	52 (26.4)	448 (36.1)	199 (31.3)	884 (44.7)
Severe	10 (13.5)	6 (9.4)	19 (9.0)	13 (6.6)	133 (10.7)	58 (9.1)	411 (20.8)
Deaths	0	0	0	1 (0.5)	2 (0.2)	4 (0.6)	18 (0.9)
Any non-fatal serious adverse event	3 (4.1)	2 (3.1)	16 (7.5)	11 (5.6)	78 (6.3)	25 (3.9)	261 (13.2)
Adverse event leading to discontinuation	6 (8.1)	0	15 (7.1)	4 (2.0)	100 (8.1)	27 (4.3)	259 (13.1)

All treated patients with epilepsy (double-blind studies)

The adverse events which occurred in more than 10 % of the patients are displayed by severity in the table below. The most common adverse events were headache (22.9 % for rufinamide vs. 18.9 % for placebo), dizziness (15.5 % vs. 9.4 %), fatigue (13.6 % vs. 9.0 %), somnolence (11.8 % vs. 9.1 %) and nausea (11.4 % vs. 7.6 %).

Table. Number (%) of patients with adverse events by preferred term (10 % of greater for either treatment group) by severity. All treated patients with epilepsy, double-blind studies)

	Rufinamide		Placebo	
	n	(%)	n	(%)
Total number of patients studied	1,240		635	
Total number of patients with an adverse event	975	(78.6)	497	(78.3)
Mild	394	(31.8)	240	(37.8)
Moderate	448	(36.1)	199	(31.3)
Severe	133	(10.7)	58	(9.1)
Headache - Total	284	(22.9)	120	(18.9)
Mild	166	(13.4)	74	(11.7)
Moderate	98	(7.9)	34	(5.4)
Severe	20	(1.6)	12	(1.9)
Dizziness - Total	192	(15.5)	60	(9.4)
Mild	117	(9.4)	46	(7.2)
Moderate	67	(5.4)	13	(2.0)
Severe	8	(0.6)	1	(0.2)
Fatigue - Total	169	(13.6)	57	(9.0)
Mild	100	(8.1)	39	(6.1)
Moderate	57	(4.6)	13	(2.0)
Severe	12	(1.0)	5	(0.8)
Somnolence - Total	146	(11.8)	58	(9.1)
Mild	98	(7.9)	44	(6.9)
Moderate	43	(3.5)	12	(1.9)
Severe	5	(0.4)	2	(0.3)
Nausea - Total	141	(11.4)	48	(7.6)
Mild	93	(7.5)	37	(5.8)
Moderate	44	(3.5)	11	(2.7)
Severe	4	(0.3)	0	

Note: Patient-years of exposure = 291.51 for rufinamide and 149.60 for placebo.

The analysis of incidence of adverse events that occurred in 10 % or more of the rufinamide-treated patients shows a general tendency for an increased incidence with increasing dose.

A safety review of eye disorders shows that such events were reported in 18, 7% of all patients who received at least 1 dose of rufinamide. The most commonly occurring eye disorders were diplopia(8,9%), vision blurred(6%) and visual disturbance among all treated patients The rate of eye disorder based on patient –years of exposure to rufinamide was higher in adults than in paediatric patients or patients with LGS. As there was a higher incidence of diplopia and blurred vision in the rufinamide group compared to placebo in controlled clinical studies and as the occurrence of diplopia and other eye disorders are common with AEDs, these findings are mentioned in the SPC (section 4.8)

- Serious adverse event/deaths/other significant events

Double-blind, adjunctive therapy study in LGS (Study 022)[n=138]

In the pivotal study in LGS, three (4.1%) rufinamide-treated patients experienced a total of 5 serious adverse events, and 2 (3.1%) placebo-treated patients experienced a total of 2 serious adverse events. Serious adverse events led to discontinuation of treatment in 1 patient, who was in the rufinamide group and had serious adverse events of vomiting, fatigue, and rash.

No patient in either treatment group died during or within 30 days of discontinuing treatment in the double-blind LGS study (Study 022).

All treated patients with epilepsy (double-blind studies)[n=1875]

Seventy-eight (6.3%) rufinamide-treated patients experienced a total of 98 serious adverse events, and 25 (3.9%) placebo-treated patients experienced a total of 28 serious adverse events. The most frequently reported serious events in the rufinamide group were related to general disorders, eye disorders and epilepsy. Fatigue was reported for 6 patients (0.5 %) in the rufinamide groups versus 0 in the placebo group. Convulsion was reported for 7 patients (0.6 %) in the active groups vs. 4 (0.6 %) in the placebo group. Status epilepticus was reported for 4 (0.3 %) in the active group vs. 0 in the placebo group.
Twenty-three serious adverse events in the rufinamide group and 7 serious adverse events in the placebo group led to discontinuation of treatment.

All treated patients with epilepsy [n=1978]
Two hundred sixty-one (13.2%) patients experienced a total of 327 serious adverse events. The estimated exposure to rufinamide in this population was 2,552.96 patient-years. The rate of serious adverse events was therefore 10.22 per 100 patient-years. The most frequently reported serious events with rufinamide were related to epilepsy: convulsion (43 patients), status epilepticus (19 patients), grand mal convulsion (11 patients), partial seizures with secondary generalization (8 patients), complex partial seizures (4 patients), epilepsy (4 patients), and partial seizures (1 patient). The most frequently occurring non-epilepsy related serious adverse events with rufinamide were pneumonia (15 patients) and vomiting (11 patients). Fifty-three serious adverse events led to discontinuation of treatment.

Deaths
Twenty-two patients (18 who received rufinamide and 4 who received placebo) died during one of the clinical studies or within 30 days after receiving the last dose of study drug in one of the studies. Six patients (2 who received rufinamide and 4 who received placebo) died during double-blind studies, and 16 died while taking rufinamide during open-label studies or open label extension studies. For all treated patients with epilepsy, the rate of deaths was 0.71 per 100 patient-years of exposure to rufinamide. The rates were 0.69 per 100 patient-years of exposure to rufinamide and 2.67 per 100 patient-years of exposure to placebo for all patients with epilepsy who received study drug in double-blind studies.
Only 1 death was suspected by the investigators of being related to study drug: cardiac arrest in Patients 0001-03008 (Study AE/ET1) who received placebo.

0101	Rufinamide	0052-00011	65/M	Death	1,200	119	Not suspected
0101	Rufinamide	0052-00016	33/M	Death	800	86	Not suspected
0101	Rufinamide	0507-00003[b]	61/F	Pneumonia, small cell carcinoma of bronchus, urinary tract infection	3,200	273	Not suspected
AE/ET1E	Rufinamide	0001-06005	64/M	Prostate cancer	1,600	NA	Not suspected
AE/ET1E	Rufinamide	0001-09009	34/F	Epilepsy	1,200	406	Not suspected
AE/ET1E	Rufinamide	0002-02056	33/F	Asphyxia	400	193	Not suspected
AE/ET1E	Rufinamide	0002-07029	48/F	Adenocarcinoma	400	504	Not suspected
AE/ET1E	Rufinamide	0008-01159	24/M	Death	1,400	173	Not suspected

[a] Dose expressed as equivalents of rufinamide.
[b] This death occurred more than 30 days after the patient received his or her last dose of rufinamide and is therefore not included in any tabulations or analyses related to deaths. A narrative is included in the CSR.

Sudden unexplained death in epilepsy (SUDEP)
The applicant has reviewed all available information concerning each of the deaths to determine which represented sudden deaths, i.e., deaths without any obvious cause (except for seizures), regardless of the investigators' terms for cause of death. Eight deaths among rufinamide-treated patients, all during open-label treatment, and the four deaths among placebo treated patients were considered sudden deaths. All deaths in the rufinamide-treated patients were considered not related to rufinamide.

- Discontinuation due to adverse events

In the double-blind studies, discontinuations due to adverse events occurred in higher percentages of rufinamide- patients (approximately 7% to 8%) than placebo-treated patients (0% to 4.3%). Discontinuations were more frequent (approximately 13%) with longer duration of rufinamide

exposure as in the open-label extensions. Of the 1,978 patients with received at least 1 dose of rufinamide, 13.1% discontinued treatment because of adverse events with the most common events being fatigue, headache, nausea, and dizziness. The reasons for discontinuations due to adverse events are reviewed below for the pivotal study 022, all double-blind studies, and for all treated patients with epilepsy.

Double-blind, adjunctive therapy study in LGS, Pivotal study 022
Six (8.1%) rufinamide-treated patients and no placebo-treated patients discontinued study drug during the double-blind study in LGS due to adverse events. The events leading to discontinuation of more than 1 patient were vomiting (3 patients), somnolence (2 patients), and rash (2 patients). No patient had laboratory abnormalities as a primary reason for discontinuation.
No patient discontinued in the placebo group.

All treated patients with epilepsy (double-blind studies)
In the population of all patients with epilepsy who received study drug in double-blind studies,
100 (8.1%) of 1,240 rufinamide-treated patients and 27 (4.3%) of 635 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 1.8% of the patients. The events most frequently leading to discontinuation of rufinamide were dizziness (22 patients), fatigue (20 patients), headache (14 patients), nausea (13 patients), and diplopia (12 patients). Rash was the cause of discontinuation for 6 (0.5%) rufinamide-treated patients and 1 (0.2%) placebo-treated patient.

The following table displays the adverse events leading to the discontinuation of more than 1 patient in either treatment group:

Table. Adverse events leading to discontinuation of more than 1 patient per treatment group (All treated patients with epilepsy, double-blind studies)

SOC	Preferred term	Rufinamide (N=1,240) N (%)	Placebo (N=635) N (%)
Any		100 (8.1)	27 (4.3)
Ear and labyrinth disorders	Vertigo	7 (0.6)	0
Eye disorders	Diplopia	12 (1.0)	1 (0.2)
	Vision blurred	3 (0.2)	1 (0.2)
	Accommodation disorder	2 (0.2)	0
Gastrointestinal disorders	Nausea	13 (1.0)	0
	Vomiting	5 (0.4)	1 (0.2)
	Abdominal pain upper	4 (0.3)	1 (0.2)
	Diarrhea	2 (0.2)	1 (0.2)
General disorders and administration site conditions	Fatigue	20 (1.6)	3 (0.5)
	Asthenia	4 (0.3)	0
	Malaise	4 (0.3)	0
	Gait disturbance	3 (0.2)	1 (0.2)
Metabolism and nutrition disorders	Anorexia	5 (0.4)	0
Nervous system disorders	Dizziness	22 (1.8)	3 (0.5)
	Headache	14 (1.1)	4 (0.6)
	Ataxia	11 (0.9)	0
	Convulsion	10 (0.8)	4 (0.6)
	Somnolence	8 (0.6)	2 (0.3)
	Nystagmus	5 (0.4)	1 (0.2)
	Paresthesia	4 (0.3)	0
	Disturbance in attention	3 (0.2)	0
	Sedation	3 (0.2)	0
	Tremor	2 (0.2)	2 (0.3)
	Hemiparesis	2 (0.2)	1 (0.2)
	Sensory disturbance	2 (0.2)	1 (0.2)
	Lethargy	2 (0.2)	0
	Grand mal convulsion	1 (0.1)	3 (0.5)
	Memory impairment	1 (0.1)	2 (0.3)
Psychiatric disorders	Anxiety	4 (0.3)	1 (0.2)
	Irritability	4 (0.3)	1 (0.2)
	Confusional state	3 (0.2)	1 (0.2)
	Apathy	3 (0.2)	0
	Aggression	2 (0.2)	1 (0.2)
	Affect lability	2 (0.2)	0
Skin and subcutaneous tissue disorders	Rash	6 (0.5)	1 (0.2)
	Face edema	2 (0.2)	0
	Rash papular	2 (0.2)	0
	Urticaria	2 (0.2)	0

Note: Patient-years of exposure = 291.51 for rufinamide and 149.60 for placebo.

All treated patients with epilepsy (n=1,978)

In the population of all treated patients with epilepsy, 259 (13.1%) of 1,978 patients treated with rufinamide discontinued study drug due to adverse events. The events most often leading to discontinuation of rufinamide were fatigue (38 patients), headache (32 patients), nausea (31 patients), dizziness (31 patients), rash (17 patients), convulsion (24), diplopia (19), somnolence (18), vomiting (13).

- Laboratory findings

Clinical laboratory data were summarized using descriptive statistics for values obtained at baseline and at the last post-baseline visit, and for the difference between those two evaluations.

Hepatic laboratory parameters

In the double-blind studies, increases in hepatobiliary parameters occurred in ≤ 3.4 % of the rufinamide-treated patients and in ≤ 6.0 % of the placebo-treated patients. For most individual parameters, the percentages of patients with upward of downward shifts were similar for rufinamide and placebo. A total of 22 cases reporting of increased liver enzymes with a value over 3N were

analysed. Although the causal role of rufinamide is difficult to establish due to confounding factors this adverse reaction will be mention inn the SPC. There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. One rufinamide-treated patient (in Study 022) discontinued due to hepatic enzymes increased. In other studies, one patient had a serious adverse event related to the hepatobiliary system (cholecystitis, Study 0101) and another patient in Study 021PE discontinued due to suspicion of hepatitis toxic, the origin of which was not confirmed later on.

Renal laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for all renal parameters, and were comparable in the rufinamide and placebo groups in the double-blind studies.

Adverse events related to renal laboratory tests or renal disorders occurred in less than 1% of all rufinamide-treated patients. One patient had a serious adverse event of renal failure acute after a prolonged seizure, which resulted in rhabdomyolysis and dehydration. Renal experts at the hospital attributed the event to the prolonged seizure, which resulted in dehydration. The patient was subsequently restarted on rufinamide.

Haematology laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable in the rufinamide and placebo groups for every population that compared results from the double-blind studies.

Thyroid laboratory parameters
Rufinamide does not appear to have a clinically or statistically significant effect on thyroid although there were individual cases of changes of T3 or TSH and individual cases of hypothyroidism.

- Other adverse effects of interest

Status epilepticus
Status epilepticus did not occur in any patient who received placebo in any of the double-blind studies in the rufinamide clinical development program. As shown in the following table, status epilepticus was an adverse event in 1.4% of all patients who received at least 1 dose of rufinamide, a serious adverse event in 1.0%, and an event that led to discontinuation of treatment in 0.3%. The incidence of status epilepticus as an adverse event was higher in patients with LGS (3.7%) and in paediatric patients (2.6%) than in adult patients (1.1%). Serious status epilepticus occurred in ≤2.0% of the patients in any subgroup, and this event led to the discontinuation of <1.0% of those in any subgroup. No patient had a status epilepticus that lead to death.

Table 7. Overview of Occurrence of Status Epilepticus in Rufinamide Clinical Studies

	Double-blind plus open-label			
	All patients with epilepsy (N=1978)	**Patients with LGS (N=135)**	**Paediatric patients (N=391)**	**Adults patients (N=1561)**
Incidence of status epilepticus	27 (1.4%)	5 (3.7%)	10 (2.6%)	17 (1.1%)
Discontinuation due to status epilepticus	6 (0.3%)	1 (0.7%)	2 (0.5%)	4 (0.3%)
Status epilepticus as non-fatal serious adverse event	19 (1.0%)	2 (1.5%)	8 (2.0%)	11 (0.7%)

Note: he population "all patients with epilepsy" includes all patients who received at least 1 dose of rufinamide in any Phase II or III double-blind study, open-label extension of a double-blind study, or open-label study. The remaining 3 populations shown in this table include all patients who received at least 1 dose of rufinamide in a Phase II or III double-blind study or its open-label extension (patients enrolled only in Phase II or III open-label studies are not included). Patients included in the population "patients with LGS" are also included in the populations "paediatric patients" and "adult patients" depending on whether their age at baseline was ≤16 years (paediatric patients) or >16 years (adult patients).
Cross reference: Appendix 3, Tables 2.2.2, 2.2.4, 2.2.6, 3.1.2, 3.2.4, 3.2.6, 5.1.1, 22.2.1, 22.4.1, 22.6.1

According to the literature, status epilepticus is a relatively frequent occurrence in paediatric patients with epilepsy. A review of the occurrence of status epilepticus in 4 epidemiologic cohorts in presented in the table below:

Incidence of Status Epilepticus in Different Epidemiologic Cohorts

	Incidence of status epilepticus	References
Rufinamide clinical trials	1.4% (27/1978)	
Rochester	9% (7/74)	Hauser 1993 Hesdorffer 1998
Finland	9% (5/53)	Sillanpaa, Jalava, Kaleva 1998 Sillanpaa, Jalava, Shinnar 1998
Bronx	11% (18/171)	Shinnar 1996
New Haven	6% (9/136)	Berg 1992 Berg 1996 Berg 1997

A review in the literature showed that status epilepticus develops in more than 60% of patients with LGS [Shorvon 1994].
As rufinamide was studied as an adjuvant therapy, the majority of exposed patients were on multiple other anti-epileptic medications. However, analysis of data shows that there is no association of any particular concomitant AED with the occurrence of status epilepticus. Except when the concomitant antiepileptic is stopped or had a dose modification, the concurrent AED could not be considered as a confounding factor in patients without a previous medical history of status epilepticus. In this particular population, rufinamide causal role in status epilepticus onset could not neither be excluded nor established. Furthermore, status epilepticus was not notified in the placebo group.
Consequently, status epilepticus is mentioned in the SPC of rufinamide, section 4.4. In addition, the applicant committed to perform a post-approval safety study (registry) which would include a sufficient number of patients to allow the estimation of adverse effects including this one.

Rash/hypersensitivity
Rash occurred in similar percentages of rufinamide-treated patients (3.1%) and placebo-treated patients (3.3%), even when the incidence was not corrected for duration of exposure. Rash was a serious adverse event in 3 (0.2%) and 1 (0.2%) patients, respectively. Rash led to discontinuation of treatment in 10 (0.8%) and 1 (0.2%) patients, respectively. Consequently, and as the majority of anti-epileptic medications are associated with rash, the mention of "Rash" in the SPC (in sections 4.4 and 4.8) and as an identified potential risk of the Pharmacovigilance plan have been included.
In all treated patients with epilepsy, rash was a serious adverse event in 5 (0.3%) patients and led to the discontinuation of treatment in 24 (1.2%) patients. None of the 1,978 patients experienced erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

In the pivotal study 022 in the Lennox-Gastatut syndrome, rash occurred more frequently in the rufinamide group than in the placebo group (6.8% for rufinamide, and 1.6% for placebo). One report of rash was classified as serious, and rash caused discontinuation of treatment in 2 patients.

In addition, a photosensitivity rash has been reported in 2 cases. These cases do not provide sufficient data to establish relationship between rufinamide therapy and the onset of photosensitivity. However, photosensitivity skin reaction could be suspected for all antiepileptic drugs.
Consequently, a warning has been included in the SPC, section 4.4 "all patients who develop a rash while taking rufinamide must be closely supervised".

Antiepileptic drug hypersensitivity syndrome
Upon review of patient narratives, the applicant suspects that a total of 5 patients (2 with serious adverse events coded as hypersensitivity and 3 others with serous adverse events coded as pyrexia or rash) might have suffered an antiepileptic drug hypersensitivity syndrome characterised by fever, rash,

and evidence of internal organ involvement. In all cases, the reaction occurred during the first 4 weeks of treatment. All patients were children. None of them had mucosal involvement or blistering of the skin. All patients recovered after discontinuation of rufinamide. After thorough analysis, the relationship with rufinamide therapy has been suspected for two of them (≈2/2000 exposed patients), which is higher than reported in the literature (≈1 per 3000 exposures). Consequently, a warning is included in the SPC in section 4.8 and a cumulative review of hypersensitivity reports will be carried out in the PSUR. The incidence of hypersensitivity will be also monitored during a post marketing safety study and included in the Pharmacovigilance plan.

Effects on weight
Rufinamide seems to induce notable weight decrease (more than 7%) in a limited number of patients under the age of 12 years. The mean weight in adult patients has not been significantly modified under rufinamide. This is mentioned as an undesirable effect in SPC and is part of the safety parameters to be monitored in the risk management plan.
The adverse event"eating disorder" which has been observed in the LGS group, is also mentioned in the SPC.

- Safety in special populations

Age
There were some differences noted between age groups. Headache, dizziness, and nausea occurred at lower rates in the youngest #group, and at comparable rates in the older groups. This was trued in both the rufinamide and placebo groups for headache and nausea, but not dizziness. Somnolence occurred at the highest rate in the youngest group of rufinamide-treated patients; rates were comparable by age in placebo-treated patients.

Gender
The incidence of common adverse events was similar for the two groups, except for nausea, which was more common in females.

Renal or hepatic impairment
A study in patients with severe renal impairment indicated that no dose adjustments are required for these patients.
Use in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

- Post marketing experience

No post-marketing data are available.

- Discussion on clinical safety

The majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (with headache, somnolence, dizziness and fatigue) and gastro intestinal disorders, with vomiting and nausea. No relationship with dose has been identified. CNS-related adverse events and gastrointestinal disorders were a common cause for treatment discontinuation.
There were no indications of ECG abnormalities or QTc prolongation associated with rufinamide exposure.

The occurrence of serious status epilepticus in the whole population of rufinamide treated patients as no case has been reported in placebo treated patients is considered a particular safety issue. Even if Status epilepticus is very frequent in patients with LGS and that 12 of the 27 patients with status epilepticus had potential triggering factors, the other cases had no obvious explanation.
This risk will be monitored in post-authorisation on long-term therapy and on a more important number of patients under rufinamide. This issue is included in the SPC and the pharmacovigilance plan.

Anticonvulsant hypersensitivity syndrome was reported in 5 patients and for 2 cases the relationship with rufinamide is suspected. A warning was introduced in the SPC. This point will be followed within each PSUR and assessed in the registry study.

At this stage, there is no strong argument for a safety issue in human regarding the risk of myelofibrosis, but we consider that this should be monitored and that a specific section in PSUR on all haematological disorders reported is deemed necessary.

Both, myelofibrosis and immunotoxic potential risks are included in the pharmacovigilance plan.

According to the CHMP guidance document concerning development of AEDs in children, short term and long-term studies should be designed to detect possible impact on learning, intelligence, growth, endocrine function and puberty. This safety aspect will be monitored as described in the risk management plan.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan that was assessed and was considered satisfactory provided that revisions are submitted to the rapporteur in the post-opinion phase (see follow-up measures)

Table Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities (routine and additional)
Status Epilepticus	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Reported Spontaneous Serious Adverse Events of seizure, or associated terms, will be followed up to exclude additional cases of status epilepticus. ▪ The registry study will evaluate the occurrence, severity and character of seizures during the use of rufinamide, and contrast these with seizures seen with other anti-epileptic drugs in patients with LGS. ▪ Seizures experienced in the registry study that are considered medically significant (require urgent change in medication, medical intervention, or hospitalization) will be reported as a serious adverse event. Therefore the diagnosis of 'status epilepticus' can be made on both historical and	▪ Status epilepticus will be described in all product labelling. ▪ In the proposed SPC status epilepticus will be described in the warning section (4.4)[1]: "Status epilepticus cases have been observed during clinical development studies, under rufinamide whereas no such cases have been observed under placebo. These events led to rufinamide discontinuation in 20 % of the cases. If patients develop new seizure types and/or experience an increased frequency of status epilepticus that is different from the patient's baseline condition, then the benefit risk ratio of the therapy should be reassessed". ▪ Status epilepticus will be

[1] As changed in SPC version 07, 8 Nov 2006

	modern criteria. Information of these events, and the full impact on the patient, will be collected through structured questions. ▪ Status epilepticus will be reviewed on a cumulative basis, and discussed in the PSUR.	included as an adverse event in Section 4.8 as a common adverse event
Hypersensitivity	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Spontaneous reported events of hypersensitivity, or associated terms, will be followed up to exclude additional cases of the Anticonvulsant Hypersensitivity Syndrome. ▪ The incidence and character of hypersensitivity reactions will be monitored during the registry study where symptoms of hypersensitivity will explicitly captured using a structured questionnaire. ▪ Assessment of the character of hypersensitivity should allow for a more accurate incidence of the 'Anticonvulsant Hypersensitivity Syndrome' during the use of rufinamide being determined. ▪ Reports of hypersensitivity reactions will be reviewed on a cumulative basis within the PSUR.	▪ Hypersensitivity will be described in the safety information. In the SPC this will be in the warning section (4.4) as: "Serious antiepileptic drug hypersensitivity syndrome has occurred in association with rufinamide therapy. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, liver function tests abnormalities, and haematuria. Because the disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. This syndrome occurred in close temporal association to the initiation of rufinamide therapy and in the paediatric population. If this reaction is suspected, rufinamide should be discontinued and alternative treatment started. All patients who develop a rash while taking rufinamide must be closely monitored". ▪ The event of hypersensitivity will be included as an uncommon adverse event in Section 4.8.
Decreased Appetite and Weight Loss	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Weight changes (when provided), compared to baseline, will be monitored during rufinamide use. Unexpected changes in weight due to confounding factors will be identified during this study, such as concomitant medications, or concurrent infections.	• Decreased appetite and weight decreased are included in Section 4.8 of the SPC as common adverse events.
Coordination Abnormal	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	• Coordination abnormal is included Section 4.8 of the SPC as a common adverse event.
Somnolence	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports	• Somnolence is included in Section 4.8 of the SPC as a very common adverse event.

	▪ Soliciting of adverse events through the registry study.	
Dizziness and vertigo	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	▪ Dizziness is included in Section 4.8 of the SPC as a very common adverse event. Vertigo is included in Section 4.8 of the SPC as a common adverse event.
Diplopia and blurred vision	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	▪ Diplopia and vertigo are included in Section 4.8 of the SPC as common adverse events.
Vomiting	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Soliciting of adverse events through the registry study.	▪ Vomiting is included in Section 4.8 of the SPC as a very common adverse event.
The risk of birth defects during pregnancy	▪ A pregnancy registry will be maintained by EURAP (European and International Registry of Anti-epileptic drugs in Pregnancy). ▪ Pregnancies will be reported in the appropriate section of the PSUR.	▪ A warning is included in Section 4.6 of the SPC. The text includes the following: "Women of childbearing potential must use contraceptive measures during treatment with Inovelon. Physicians should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patients clinical situation (see Section 4.5). ▪ If women treated with rufinamide plan to become pregnant, the indication of this product should be carefully weighed. During pregnancy, an effective antiepileptic rufinamide treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus".
Potential for haematological blood dyscrasias	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Review of provided laboratory values provided during the registry study. ▪ Soliciting of adverse events through the registry study. ▪ Haematological adverse events will be addressed in the PSUR.[2]	▪ Pre-clinical findings are discussed in Section 5.3 of the SPC: "Adverse effects not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to human use was myelofibrosis of the bone marrow in the mouse carcinogenicity study".

[2] As requested by the CHMP

Potential for immuno-toxicity	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Review of provided laboratory values provided during the registry study. ▪ Soliciting of adverse events through the registry study. ▪ Immune disorders and associated haematological adverse events will be addressed in the PSUR.	▪ Pre-clinical findings are discussed in Section 5.3 of the SPC: "Regarding the immunotoxic potential, small thymus and thymic involution were observed in dogs in a 13 week study with significant response at the high dose in male. In the 13 week study, female bone marrow and lymphoid changes are reported at the high dose with a weak incidence.–In rats decreased cellularity of the bone marrow and thymic atrophy were observed only in the carcinogenicity study". ▪ Infections frequently experienced during the LGS study are included in the SPC as common adverse events in Section 4.8 (Pneumonia, influenza, nasopharyngitis, ear infection, sinusitis and rhinitis)
Potential for the developmental and maturation impairment in children and adolescents	▪ Review of basic growth measurements, when provided, during the registry study. ▪ Soliciting of adverse events through the registry study.	
Potential for adverse effect on cognition	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Soliciting of adverse events through the registry study. ▪ Analysis of discontinuations form the registry study for events associated with cognitive impairment.	▪ Somnolence and dizziness are included as very common adverse events in Section 4.8 of the SPC.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Additionally, further safety information will be collected in a post-marketing safety study (registry) of anti-epileptic drugs in LGS.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

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 potential 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.

Efficacy
For efficacy, the results of the single pivotal study to assess the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome showed positive results in LGS as compared to placebo.
The patient population, as chosen on the basis of the inclusion/exclusion criteria, was appropriate and representative of patients with LGS, in particular due to the substantial proportion of children included in the present trial (more than 2/3).
Patients who received rufinamide in this trial showed:

- a significant median reduction in total seizure and tonic-atonic seizure frequency compared to placebo;
- a significant improvement in the severity of the seizures compared to placebo;
- significantly greater (50% and 75%) responder rates for tonic-atonic seizure frequency per 28 days versus placebo;
- greater reductions in all seizure types associated with LGS (absence, tonic-clonic, myoclonic, tonic, atonic, partial) compared to placebo.

The sensitivity analysis performed confirmed the robustness of the results.

Nevertheless, the assessment of the impact of the baseline imbalance on the total seizure frequency could not be totally excluded.
Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.
Supportive studies with rufinamide permitted to collect data about titration, maintenance dose, dose-response relationship, pharmacokinetics and short term safety.

Safety
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics
The majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (headache, somnolence, dizziness and fatigue) and gastro intestinal disorders (vomiting and nausea). No relationship with dose has been identified.

Status epilepticus and anticonvulsant hypersensitivity syndrome will be followed up in the pharmacovigilance plan.

At this stage, there is no strong argument for a safety issue in human regarding the potential risk of myelofibrosis, the CHMP considers that this should be monitored and a specific section on all haematological disorders will be reported in the PSUR.

Immunotoxic potential risk is included in the pharmacovigilance plan. (see follow-up measures)

Having considered the safety concerns listed in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The results of the user testing were assessed and a number of insufficiencies were noted. Consequently, the applicant proposed to implement several improvements to the package leaflet.

Risk-benefit assessment

For efficacy, the results of the single pivotal study to assess the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome showed positive results in LGS as compared to placebo.
Supportive studies with rufinamide permitted to collect data about titration, maintenance dose, dose-response relationship, pharmacokinetics and short term safety.
The sensitivity analysis performed confirmed the robustness of the results.
Nevertheless, the assessment of the impact of the baseline imbalance on the total seizure frequency could not be totally excluded.
Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.
On the safety aspects, the majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (headache, somnolence, dizziness and fatigue) and gastro intestinal disorders (vomiting and nausea). No relationship with dose has been identified.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

Since effects on skeletal, behavioural, sexual, immune maturation and development in the population of young patients suffering Lennox Gastaut syndrome could induce more consequences on their general vulnerable state and that rufinamide will be used as add-on drug, monitoring of body weight, height , general growth including puberty, cognitive state before and after drug initiation will be addressed as outlined in the planned post-approval study that is integrated in the risk management plan.
The following safety issues will be specifically monitored:

- Status epilepticus
- Hypersensitivity
- Decreased appetite and weight loss

    - Coordination abnormal
    - Somnolence
    - Dizziness and vertigo
    - Diplopia and blurred vision
    - Vomiting
    - The risk of birth defects with anti-epileptic drugs
    - Potential for haematological blood dyscrasias
    - Potential for immuno-toxicity
    - Potential for developmental and maturation impairment in children and adolescents
    - Potential for adverse effect on cognition
    - The risk of suicide with anti-epileptic drugs
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Inovelon, in the treatment of "seizures associated with Lennox-Gastaut syndrome as adjunctive therapy in patients 4 years and older", was favourable and therefore recommended the granting of the marketing authorisation.