

Rufinamide for the treatment of Lennox-Gastaut syndrome: evidence from clinical trials and clinical practice

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ABSTRACT – Rufinamide was granted orphan drug status in 2004 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients aged ≥ 4 years, and was subsequently approved for this indication in several countries, including Europe and the United States. Structurally unrelated to other antiepileptic drugs, rufinamide is thought to act primarily by prolonging the inactivation phase of voltage-gated sodium channels. Rufinamide was approved on the basis of an international, randomised, placebo-controlled Phase III trial, conducted in 138 patients with Lennox-Gastaut syndrome, which demonstrated its favourable tolerability profile and efficacy in significantly reducing the frequency of drop attacks and total seizures, compared with placebo. The effectiveness and safety/tolerability of rufinamide in treating seizures associated with Lennox-Gastaut syndrome have subsequently been confirmed in several other clinical trials and long-term extension studies. These findings are supported by 'real-world' data from a series of clinical practice studies conducted in Europe, the United States, and Korea. Rufinamide has been shown to be effective and generally well tolerated in children as young as one year and in adults. It is particularly effective as treatment for drop attacks and generalised tonic-clonic seizures, and it has been suggested that it might be preferred over other antiepileptic drugs as a second-line treatment for Lennox-Gastaut syndrome when drop attacks are frequent. The most common side effects of rufinamide treatment include somnolence, headache, dizziness, nausea, vomiting, and fatigue. No new or unexpected safety signals have emerged following long-term treatment with rufinamide, either in clinical trials or in clinical practice.

Key words: antiepileptic drug, drop attack, epilepsy, epileptic encephalopathy, Lennox-Gastaut syndrome, rufinamide

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Lennox-Gastaut syndrome (LGS) is a severe, chronic, epileptic encephalopathy that is associated with considerable morbidity and mortality (Arzimanoglou and Resnick, 2011a). LGS is characterised by a triad of features, comprising [1] multiple seizure types that include tonic seizures, [2] abnormal EEG features with slow spike-wave discharges, and [3] cognitive impairment that is often accompanied by behavioural problems (Arzimanoglou *et al.*, 2009). Although accurate and early diagnosis of LGS is crucial for its effective treatment and management, this is often challenging, primarily because not all of the characteristic features of LGS are found in every case and the features evolve and change over time (Arzimanoglou *et al.*, 2009; Arzimanoglou and Resnick, 2011a). Furthermore, since other types of seizures and EEG features can occur alongside the 'typical' features of the condition, LGS may often be confused with other syndromes, particularly during its early stages (Arzimanoglou and Resnick, 2011a).

LGS constitutes a major burden for patients and their families, necessitating a multidisciplinary, individualised approach to care that addresses each patient's medical, educational, psychological, and social needs, throughout the course of their life (Arzimanoglou and Resnick, 2011b). In order to help control the multiple seizure types associated with LGS, antiepileptic drugs (AEDs) are often used in a variety of combinations; however, the use of polytherapy increases the risk of adverse effects and may aggravate existing co-morbidities (Arzimanoglou and Resnick, 2011b). AEDs used to treat LGS include valproic acid, lamotrigine, topiramate, clobazam, felbamate, and rufinamide (Arzimanoglou *et al.*, 2009; Montouris *et al.*, 2014; Cross *et al.* 2017). Non-pharmacological treatment approaches include vagus nerve stimulation, electrical stimulation of the centromedian thalamic nucleus, and use of the ketogenic diet (Arzimanoglou *et al.*, 2009). However, even with advanced non-pharmacological treatment modalities, including surgery, it is not necessarily possible to provide adequate seizure control for patients with LGS (Kim *et al.*, 2015).

Rufinamide is a triazole derivative, structurally unrelated to other AEDs (Jain, 2000), and was granted orphan drug status in 2004 for the adjunctive treatment of seizures associated with LGS in patients aged ≥ 4 years (Resnick *et al.*, 2011). It was subsequently approved for this indication in several countries, including Europe and the US (Inovelon[®] Summary of Product Characteristics, 2017; Banzel[®] Prescribing Information, 2017). A consensus of expert opinion recommended that broad-spectrum AEDs, such as valproate, benzodiazepines, and lamotrigine, should be used in the early stages of LGS, and that lamotrigine, topiramate, felbamate, and rufinamide should be considered for the treatment of drop attacks during

the state (as opposed to onset stage) of the disorder (Arzimanoglou *et al.*, 2009; Cross *et al.*, 2017). Other published treatment algorithms for LGS have recommended first-line therapy with valproate (van Rijckevorsel, 2008; Ferrie and Patel, 2009), together with adjunctive therapy with either topiramate, lamotrigine, or rufinamide, followed by felbamate (van Rijckevorsel, 2008), or one or two of lamotrigine, topiramate, rufinamide, levetiracetam, and zonisamide (Ferrie and Patel, 2009). A Cochrane review of randomised controlled trials of treatments for LGS concluded that although the optimum treatment for LGS remains uncertain, rufinamide, lamotrigine, topiramate, and felbamate may be useful as add-on therapy for the condition and clobazam may be helpful against drop seizures (Hancock and Cross, 2013). Since rufinamide is particularly effective in decreasing the frequency of tonic and atonic seizures (drop attacks), it has also been suggested that it might be preferred to other AEDs as a second-line treatment for LGS when drop attacks are frequent (Coppola *et al.*, 2014). Notably, rufinamide also seems to be a promising therapeutic option for myoclonic-atonic seizures in patients with Doose syndrome (another form of epileptic encephalopathy), with sustained efficacy in over half of patients and a favourable tolerability profile (von Stülpnagel *et al.*, 2012). The objective of this article is to provide an overview of the pharmacology of rufinamide, and an update on evidence from clinical trials and 'real-world' clinical practice relating to its efficacy and safety/tolerability in the treatment of LGS, including treatment in the adult setting.

Methodology for literature review of clinical evidence for rufinamide in LGS

Articles published up to March 2017 relating to the use of rufinamide to treat LGS patients were identified from PubMed using the search term 'rufinamide'. Articles reporting case reports (≤ 3 patients) and/or published in languages other than English were excluded. All other articles reporting on the efficacy/effectiveness and safety/tolerability of rufinamide when used to treat LGS patients in clinical trials or clinical practice studies were included.

Rufinamide pharmacology

Mode of action

The principal mode of action of rufinamide is thought to be via limiting the firing of sodium-dependent action potentials (Hakimian *et al.*, 2007). Experimental models indicate that rufinamide suppresses neuronal hyperexcitability by prolonging the inactivation phase

of voltage-gated sodium channels (McLean *et al.*, 2005; Perucca *et al.*, 2008). At clinically relevant concentrations, rufinamide has also been shown to inhibit activation of the human voltage-gated sodium channel type I alpha subunit (Na_v1.1; SCN1A), a distinct mechanism of action among anticonvulsants (Gilchrist *et al.*, 2014) that might also explain its lack of efficacy or worsening effect in patients with a genetically determined loss-of-function of SCN1A (Dravet syndrome) (Mueller *et al.*, 2011). *In vitro* studies have demonstrated that, at relatively high concentrations, rufinamide exhibits an inhibitory effect on the human recombinant metabotropic glutamate receptor subtype 5 (mGluR5), which might also influence its anticonvulsant activity (Perucca *et al.*, 2008). In contrast, rufinamide does not appear to interact with the mGluR1b, mGluR2, and mGluR4 subtypes; benzodiazepine or gamma-aminobutyric acid receptors; 5-HT₁ and 5-HT₂ receptors; or α - or β -adrenoceptors (Perucca *et al.*, 2008). In rodent seizure models, rufinamide has been shown to suppress seizures induced by maximal electroshock and, at higher doses, chemically-induced seizures, with a higher protective index than that of the other AEDs tested (ethosuximide, phenobarbital, phenytoin, and valproate) (White *et al.*, 2008). Interestingly, in a multicentre, double-blind, placebo-controlled, randomised, parallel-group trial of rufinamide (1,600 mg twice daily) in adults and adolescents (aged ≥ 16 years) with refractory partial seizures, there was a 12.3% reduction in monthly seizure frequency in the 96 patients established on carbamazepine (p =not significant vs. placebo), compared with a 29.2% reduction in the 60 patients taking a regimen that did not contain carbamazepine (p =0.05 vs. placebo) (Brodie *et al.*, 2009). Arguably, this observation could suggest that carbamazepine and rufinamide have similar effects on voltage-dependent sodium channels, although the possibility that carbamazepine may have decreased plasma concentrations of rufinamide through enzyme induction cannot be ruled out (Perucca *et al.*, 2008).

Dosing and pharmacokinetics

Rufinamide is administered orally and dosed according to age, weight, and concomitant use of valproate (Inovelon[®] Summary of Product Characteristics, 2017). In children aged ≥ 4 years, weighing <30 kg, it is recommended that rufinamide should be initiated at 200 mg/day and increased by 200-mg/day increments as frequently as every two days to a maximum recommended dose of 1,000 mg/day in patients not receiving valproate and 600 mg/day in those receiving valproate (Inovelon[®] Summary of Product Characteristics, 2017). In adults, adolescents, and children ≥ 4 years weighing >30 kg, it is recommended

Table 1. Pharmacokinetic profile of rufinamide. Adapted from Perucca *et al.*, 2008.

Bioavailability*	$\geq 85\%$
Time to maximum plasma concentration	4-6 h
Plasma half-life	6-10 h
Plasma protein binding	26-35% [†]
Volume of distribution [‡]	
3,200 mg/day	52.7 l (0.8 l/kg)
7,200 mg/day	81.6 l (1.2 l/kg)
Metabolism	
Route	Hepatic
Proportion unmetabolised	$<2\%$
Excretion route	Predominantly renal
Apparent clearance at steady state	3-5.6 l/h [§]

*Following a 600-mg dose.

[†]Mostly limited to serum albumin.

[‡]For a subject weighing 67 kg with a body surface area of 1.79 m².

[§]Depending on body size (clearance being slower in children than in adults).

that rufinamide should be initiated at 400 mg/day and increased by 400-mg/day increments as frequently as every two days, up to a maximum recommended dose of 1,800-3,200 mg/day, depending on body weight (Inovelon[®] Summary of Product Characteristics, 2017). Gastrointestinal absorption of rufinamide is enhanced in the presence of food (Inovelon[®] Summary of Product Characteristics, 2017). At a relatively low dose (600 mg), over 85% of the administered drug is recovered in urine, predominantly as active metabolites, but bioavailability decreases with increasing dose (table 1) (Perucca *et al.*, 2008). Rufinamide undergoes extensive metabolism, primarily via hydrolysis of the carboxylamide group to a pharmacologically inactive derivative (Inovelon[®] Summary of Product Characteristics, 2017). It is not metabolised to any notable degree by cytochrome P450 enzymes (Inovelon[®] Summary of Product Characteristics, 2017). The pharmacokinetic profile of rufinamide is unaffected by sex, renal impairment, or old age (Inovelon[®] Summary of Product Characteristics, 2017). Pooled population pharmacokinetic/pharmacodynamic analyses have demonstrated a positive correlation between plasma rufinamide concentrations and improved seizure frequency (Perucca *et al.*, 2008). Similarly, plasma rufinamide concentrations were found to be higher in patients with adverse events (AEs) than in those without AEs (Perucca *et al.*, 2008).

Interaction with other agents

Rufinamide does not inhibit the activity of cytochrome P450 enzymes, but has a modest to moderate inductive effect on CYP3A4 (Inovelon® Summary of Product Characteristics, 2017). Rufinamide reduces the plasma concentrations of triazolam, ethinyl oestradiol, and norethisterone, but appears not to have a clinically relevant effect on steady-state concentrations of carbamazepine, lamotrigine, phenobarbital, topiramate, phenytoin, or valproate (Inovelon® Summary of Product Characteristics, 2017). Rufinamide plasma concentrations are increased by valproate, particularly in patients with low body weight (<30 kg), which is why rufinamide dose reduction should be considered in patients weighing <30 kg who are receiving valproate therapy (Inovelon® Summary of Product Characteristics, 2017). Oxcarbazepine and methsuximide may decrease serum rufinamide concentrations (May *et al.*, 2011). No significant changes in rufinamide concentration are observed when it is co-administered with lamotrigine, topiramate, or benzodiazepines (Perucca *et al.*, 2008).

Rufinamide in clinical trials

Rufinamide obtained marketing authorisation on the basis of an international, multicentre, randomised, double-blind, placebo-controlled trial, in which 138 LGS patients, aged 4–37 years, received adjunctive therapy with either rufinamide ($n=74$) or placebo ($n=64$) (Glauser *et al.*, 2008). After 12 weeks of double-blind treatment, patients who received rufinamide experienced a significant reduction in drop attacks (tonic-atonic seizures) compared with those who received placebo (-42.5% vs. $+1.4\%$; $p<0.0001$) and a significant reduction in total seizures (-32.7% vs. -11.7% ; $p=0.0015$). Rufinamide also significantly reduced the frequency of absence and atypical absence seizures (-50.6 vs. -29.8 ; $p=0.0222$) and atonic seizures (-44.8 vs. -21.0 ; $p=0.0125$), compared with placebo. The responder rate (with response defined as $\geq 50\%$ seizure frequency reduction from baseline) was significantly higher for patients receiving rufinamide versus placebo for both drop attacks (42.5% vs. 16.7% ; $p=0.002$; *figure 1A*) and total seizures (31.1% vs. 10.9% ; $p=0.0045$; *figure 1A*). In addition, a significantly higher proportion of patients treated with rufinamide reported a decrease in seizure severity compared with placebo (53.4% vs. 30.6% ; $p=0.0041$). Rufinamide was generally well tolerated and the most commonly reported AEs (reported by $\geq 10\%$ of patients receiving rufinamide) were somnolence (24.3% with rufinamide vs. 12.5% with placebo), vomiting (21.6% vs. 6.3%), and pyrexia (13.5% vs. 17.2%) (Glauser *et al.*, 2008). The trial was followed by a long-

term, open-label extension study, in which all patients ($n=124$) received rufinamide for a median of 432 days (range: 10–1,149 days) (Kluger *et al.*, 2010a). Reductions in seizure frequency were maintained throughout the study; during the last 12 months of treatment, 47.9% and 41.0% of patients experienced $\geq 50\%$ reduction from baseline in the frequency of drop attacks and total seizures, respectively (*figure 1B*), and 6.8% of patients became free of drop attacks. Tolerability observed in the initial trial was also maintained with long-term treatment and the most commonly reported AEs were vomiting (30.6%) and pyrexia (25.8%) (Kluger *et al.*, 2010a).

A multicentre, randomised, double-blind, placebo-controlled trial was conducted in Japan, in which LGS patients, aged 4–30 years, were randomised to 12 weeks of double-blind treatment with adjunctive rufinamide ($n=29$) or placebo ($n=30$) (Ohtsuka *et al.*, 2014). Similar to the initial Phase III trial (Glauser *et al.*, 2008), this demonstrated that rufinamide was associated with significantly greater reductions from baseline (vs. placebo) in the frequency of both tonic-atonic seizures (-24.2% vs. -3.3% ; $p=0.003$) and total seizures (-32.9% vs. -3.1% ; $p<0.001$; *figure 2*) (Ohtsuka *et al.*, 2014). Rufinamide also significantly reduced the frequency of tonic ($p=0.031$), myoclonic ($p=0.021$), and partial seizures ($p=0.025$), compared with placebo. Multiple regression analysis revealed that no factors independently affected the efficacy of rufinamide, including sex, age, seizure type, transition from West syndrome, concomitant AEDs, and baseline frequency of tonic-atonic seizures. All AEs were mild to moderate in severity and the most frequently reported rufinamide-related AEs were somnolence (17.2%), decreased appetite (17.2%), and vomiting (13.8%) (Ohtsuka *et al.*, 2014). Fifty-four patients from this trial continued into an open-label extension study during which all patients received adjunctive rufinamide (Ohtsuka *et al.*, 2016). Seizure frequency was evaluated until 52 weeks after the start of the extension study and AEs were evaluated throughout. Approximately 70% of patients were retained on rufinamide therapy for >2 years. Reductions in the frequency of tonic-atonic and total seizures from the baseline of the initial randomised controlled trial were maintained over 52 weeks of treatment (median percentage reduction from baseline at 52 weeks: -36.1% for tonic-atonic seizures and -47.4% for total seizures). At last observation, the responder rate ($\geq 50\%$ seizure frequency reduction from the baseline of the initial trial) was 39.1% for tonic-atonic seizures and 43.5% for total seizures, and seizure freedom rates ranged from 2.2% for total seizures to 57.1% for myoclonic seizures. AEs were mild or moderate in intensity, except for transient seizure aggravation in three patients (including non-convulsive status epilepticus in two patients). The most

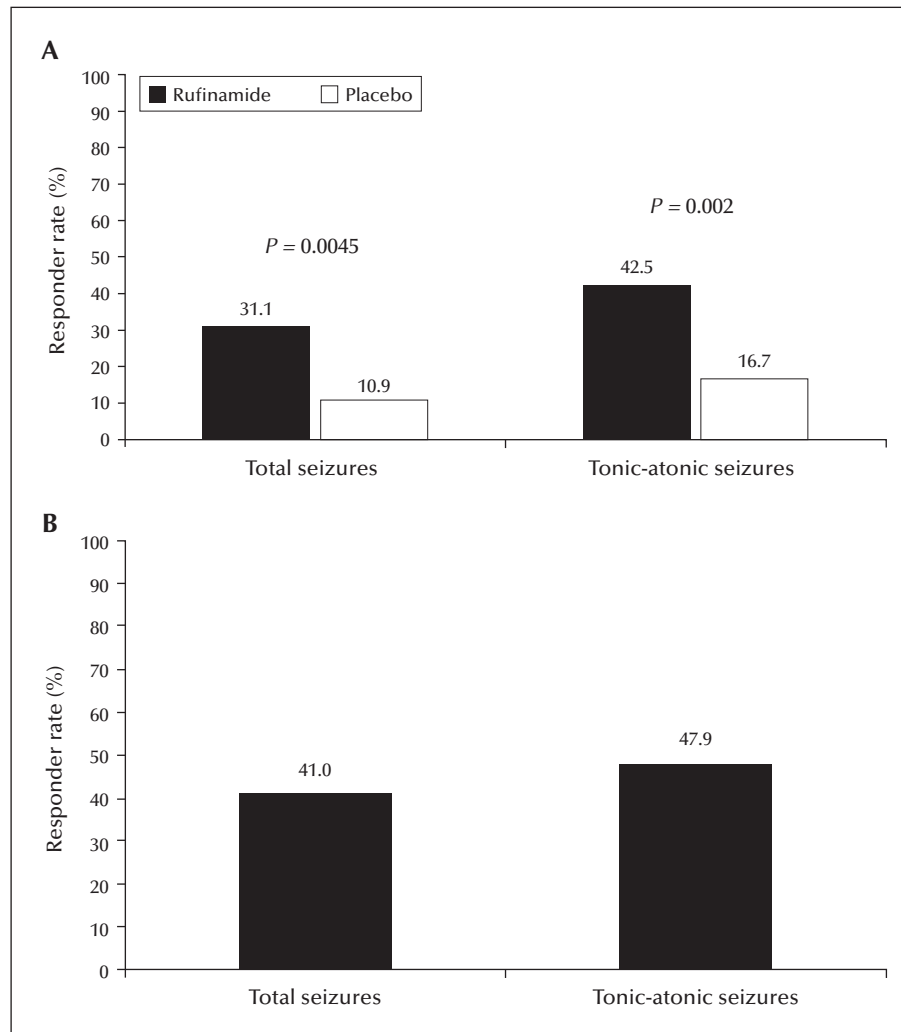


Figure 1. Responder rates for total seizures and tonic-atonic seizures in (A) the original Phase III trial and (B) the long-term extension study of the original Phase III trial. Response was defined as $\geq 50\%$ seizure frequency reduction from baseline. Figure 1A adapted from Glauser *et al.*, 2008 ; figure 1B adapted from Kluger *et al.*, 2010a.

frequent treatment-related AEs were somnolence (20.4%), decreased appetite (16.7%), transient seizure aggravation (13.0%), vomiting (11.1%), and constipation (11.1%). Although weight loss was reported as an AE in only three patients, 40.7% of patients experienced clinically notable weight loss (defined as $\geq 7\%$ relative to baseline) at least once during long-term observation (Ohtsuka *et al.*, 2016).

In addition, an open-label, observational trial, conducted in Korea, investigated the efficacy and safety/tolerability of adjunctive rufinamide in 128 patients with intractable LGS, aged 1.8-19.9 years (Kim *et al.*, 2012a). Following 16 weeks of treatment (four weeks titration, 12 weeks maintenance treatment), the retention rate was 87.5%, the responder rate was 35.9% (response defined as $>50\%$ seizure frequency

reduction), the seizure freedom rate was 7.8%, and the overall seizure reduction rate was 31.7%. The percentage of patients experiencing $>50\%$ reduction in the frequency of convulsive seizures, drop attacks, myoclonic seizures, and spasms was 39.4%, 36.4%, 33.3%, and 20.0%, respectively. Overall, 16.4% of patients experienced a worsening of seizure frequency or intensity. AEs, which were reported for 32.8% of patients overall, were mostly of mild severity and transient in nature. The most commonly reported AEs were fatigue (11.7%) and poor appetite (7.0%) (Kim *et al.*, 2012a).

A Phase III, multicentre, randomised, active-controlled, open-label, two-year study has evaluated the safety, pharmacokinetics, and cognitive/behavioural effects of rufinamide as adjunctive treatment for children aged ≥ 1 to <4 years with

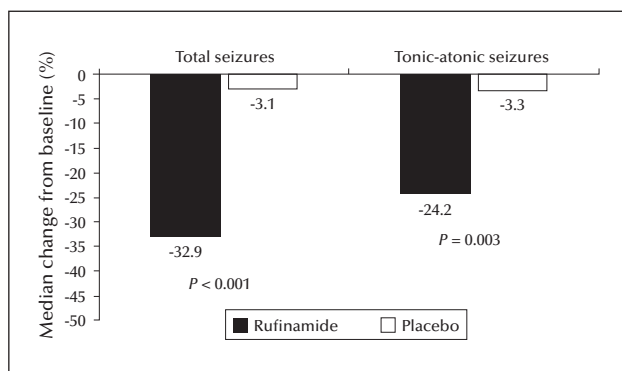


Figure 2. Median percentage change from baseline in 28-day frequency of total and tonic-atonic seizures in a randomised, double-blind, placebo-controlled trial conducted in Japan. Adapted from Ohtsuka *et al.*, 2014.

inadequately controlled LGS (Arzimanoglou *et al.*, 2016). The trial included 37 patients who were randomised to receive either rufinamide or any other approved AED chosen by the investigator as adjunctive therapy to their existing regimen of one to three AEDs. A six-month interim safety and pharmacokinetic analysis demonstrated that the incidence of treatment-emergent AEs was similar in patients treated with rufinamide (88.0%) and other AEDs (81.8%). In both groups, the majority of AEs were of mild or moderate intensity. In the rufinamide group, the most frequently reported AEs (reported by $\geq 10\%$ of patients) were vomiting (24.0%), upper respiratory tract infections (20.0%), diarrhoea and somnolence (16.0% each), and constipation, cough, bronchitis, rash, and decreased appetite (12.0% each). Results of the pharmacokinetic analysis demonstrated that rufinamide's pharmacokinetic profile in patients aged ≥ 1 to < 4 years is comparable with the profile in patients aged ≥ 4 years (Arzimanoglou *et al.*, 2016).

Rufinamide in clinical practice

The efficacy and safety/tolerability of adjunctive rufinamide as treatment for LGS in clinical practice has been investigated in a number of studies in Europe, the US, and Korea (table 2).

European experience

A retrospective observational study, conducted in eight sites across Germany and Austria, investigated the clinical course of patients treated with rufinamide for refractory epilepsy, including 31 patients with LGS (mean age: 9.4 years; range: 1.9–50.2 years) (Kluger *et al.*, 2009; Resnick *et al.*, 2011). Over a 12-week observation period, 54.8% of LGS patients were responders: 25.8% experienced 50–75% seizure frequency

reduction, 16.1% experienced 75–99% seizure frequency reduction, and 12.9% achieved seizure freedom during the last four weeks of observation. Of the patients with LGS, 51.6% experienced AEs (Resnick *et al.*, 2011). Most AEs were mild to moderate in intensity and no serious AEs were reported (Kluger *et al.*, 2009). All 31 LGS patients continued into a long-term follow-up study, during which rufinamide treatment in the overall population was extended for a mean duration of 14.5 months (Kluger *et al.*, 2010b). The retention rate for LGS patients was 51.6% and 35.5% were responders (as assessed during the last four weeks of the observation period). Rufinamide was well tolerated during long-term treatment (Kluger *et al.*, 2010b).

A long-term, prospective, add-on, open-label study was also conducted in 43 LGS patients recruited from 11 centres in Italy (Coppola *et al.*, 2010). During a mean follow-up duration of 12.3 months, 60.5% of patients were responders and 9.3% achieved seizure freedom. AEs were reported for 23.2% of patients while taking rufinamide; these were vomiting and/or gastrointestinal problems ($n=6$), irritability/aggressiveness ($n=3$), drowsiness ($n=1$), skin rash ($n=1$), and decreased appetite ($n=1$). Three patients discontinued rufinamide due to vomiting; otherwise, AEs were mild and transient (Coppola *et al.*, 2010).

A retrospective study conducted at a single epilepsy centre in France examined the efficacy and tolerability of adjunctive rufinamide in 10 LGS patients (mean age: 10.5 years) (Auvin *et al.*, 2014a). All patients were treated with one to four concomitant AEDs and all received concomitant valproate therapy (Auvin *et al.*, 2014a). Overall, nine of 10 patients responded to rufinamide treatment (Auvin *et al.*, 2014a). During titration, eight of nine responders experienced seizure aggravation, which resolved with down-titration to a lower maintenance dose (Auvin *et al.*, 2014a). The patient who did not respond to rufinamide treatment experienced a tonic-clonic seizure one month after initiation of rufinamide therapy, which was therefore discontinued (Auvin *et al.*, 2014b). Among responders, rufinamide was generally well tolerated (Auvin *et al.*, 2014b).

A multicentre, retrospective chart review was conducted of 58 patients (median age: 29.4 years) prescribed adjunctive rufinamide at seven Spanish epilepsy centres, 37 of whom (63.8%) were diagnosed with LGS or generalised epilepsy with impaired mental development; the remaining 21 patients had focal epilepsies, mainly frontal lobe ($n=13$) (Jaraba *et al.*, 2016). The rufinamide retention rate after 12 months was 56.9% in the overall population and 64% in patients with LGS. Overall, 20.7% of patients discontinued rufinamide due to lack of efficacy and 8.6% due to AEs. Of 19 patients who had tonic-clonic seizures and remained on treatment at 12 months, six (31.6%) became seizure-free and 14 (73.7%) were responders.

Table 2. Summary of studies conducted in Europe, the USA, and Korea, in which rufinamide was used as adjunctive therapy to treat LGS patients in clinical practice.

Authors	Study design	Population	Rufinamide dosing	Follow-up	Key efficacy findings	Key tolerability findings
Europe						
Kluger <i>et al.</i> (Kluger <i>et al.</i> , 2009; Resnick <i>et al.</i> , 2011)	Retrospective, observational; 8 centres in Germany and Austria	60 patients with severe refractory epilepsies (mean age: 14.5 years; range: 1-50 years); 31 with LGS	LGS patients: • Initiated at 10 mg/kg/day • Mean maintenance dose: 34.4 mg/kg/day (range: 10.0-85.7 mg/kg/day) • Maintenance dose generally achieved within 4 weeks	12-week observation period	LGS patients: • Total seizure responder rate*: 54.8% • Seizure freedom rate: 12.9%	LGS patients: • 51.6% experienced AEs Overall population: • 58.3% experienced AEs • Most common AEs: fatigue (18.3%), vomiting (13.3%), loss of appetite (10.0%), and behavioural disturbances (8.3%) • Most AEs mild to moderate in intensity • No serious AEs reported
Kluger <i>et al.</i> (Kluger <i>et al.</i> , 2010b; Resnick <i>et al.</i> , 2011)	Long-term follow-up study of Kluger <i>et al.</i> (2009)	52 patients with severe refractory epilepsies (mean age: 14.9 years; range: 1-50 years); 31 with LGS	LGS patients: • Median maintenance dose: 34.0 mg/kg/day (range: 16.0-83.0 mg/kg/day)	Mean duration: 14.5 months (range: 3-18 months)	LGS patients: • Retention rate: 51.6% • Total seizure responder rate*: 35.5%	Overall population: • Generally well tolerated • Most common AEs: fatigue (18.3%), vomiting (15.0%), and loss of appetite (10.0%) • Most AEs occurred during titration and subsided during maintenance dosing • No serious treatment-related AEs reported
Coppola <i>et al.</i> (Coppola <i>et al.</i> , 2010)	Long-term, prospective, open-label study; 11 centres in Italy	43 LGS patients (mean age: 15.9 years; range: 4-34 years)	• Initiated at 10 mg/kg/day • Mean final dose: 33.5 mg/kg/day (range: 11.5-60 mg/kg/day) with VPA; 54.5 mg/kg/day (range: 21.8-85.6 mg/kg/day) without VPA	Mean duration: 12.3 months (range: 3-21 months)	• Total seizure responder rate*: 60.5% • Seizure freedom rate: 9.3%	• 23.2% experienced AEs • Most common AEs: vomiting and/or GI problems ($n=6$); irritability/aggressiveness ($n=3$) • 3 patients discontinued due to AEs (vomiting)

Authors	Study design	Population	Rufinamide dosing	Follow-up	Key efficacy findings	Key tolerability findings
Auvin <i>et al.</i> (Auvin <i>et al.</i> , 2014a; Auvin <i>et al.</i> , 2014b)	Single-centre, retrospective study in France	10 LGS patients (age range: 3-16 years)	Among responders: • Mean (range) initiation dose: 2.6 (0.8-5.0) mg/kg/day • Mean (range) titration: 12.6 (4.0-20.0) weeks • Mean (range) maintenance dose: 7.9 (3.0-17.5) mg/kg/day • All patients received concomitant VPA (mean dose: 27.2 mg/kg/day)	Not specified	<ul style="list-style-type: none"> • Total seizure responder rate*: 90% • During titration, 8/9 responders experienced seizure aggravation, which resolved with down-titration to a lower maintenance dose 	Generally well tolerated among responders
Jaraba <i>et al.</i> (Jaraba <i>et al.</i> , 2016)	Multicentre, retrospective chart review in Spain	58 patients (median age: 29.4 years; range: 7-57 years); 37 with LGS or generalised epilepsy with impaired mental development (median age: 9.7 years; range: 7-57 years)	Mean dose: 26.0 mg/kg/day (range: 5-66.7 mg/kg/day)	12 months	<p>LGS patients:</p> <ul style="list-style-type: none"> • 12-month retention rate: 64% <p>Overall population:</p> <ul style="list-style-type: none"> • 12-month retention rate: 56.9% • Tonic/atonic seizure responder rate*: 56.7% • Tonic/atonic seizure freedom rate: 16.7% • Tonic-clonic seizure responder rate*: 73.7% • Tonic-atonic seizure freedom rate: 31.6% 	<p>Overall population:</p> <ul style="list-style-type: none"> • 36.2% experienced AEs • Most common AEs: nausea, vomiting, and weight loss • No severe AEs reported

Authors	Study design	Population	Rufinamide dosing	Follow-up	Key efficacy findings	Key tolerability findings
Grosso <i>et al.</i> (Grosso <i>et al.</i> , 2014)	Multicentre, open, retrospective, pragmatic study; 8 centres in Italy	40 children aged <4 years with drug-resistant epilepsy syndromes (mean age: 39.5 months; range: 22-48 months); 4 with LGS	Mean dose: 31.5 mg/kg/day (range: 27-33.2 mg/kg/day) with VPA; 44.2 mg/kg/day (range: 41.2-47.1 mg/kg/day) without VPA	Mean duration: 12.2 months (range: 5-21 months)	LGS patients: • Total seizure responder rate [†] : 50% Overall population: • Total seizure responder rate [†] : 27.5% • Seizure freedom rate: 5% • Seizure reduction by seizure type: epileptic spasms, 46%; drop attacks, 42%; tonic seizures, 35%; focal motor seizures, 30%	Overall population: • 37.5% experienced AEs • Most common AEs: vomiting (15%), drowsiness and nervousness (12.5%), anorexia, and weight loss (10%) • Patients discontinued due to worsening of seizure frequency (<i>n</i> =4) and AEs (<i>n</i> =2)
USA						
Vendrame <i>et al.</i> (Vendrame <i>et al.</i> , 2010; Resnick <i>et al.</i> , 2011)	Single-centre, retrospective, observational study	77 patients with refractory epilepsy (median age: 12 years; range: 1-27 years); 26 with LGS	LGS patients: • Median starting dose: 9.2 mg/kg/day • Median maintenance dose: 42.1 mg/kg/day • Median time to reach maximum dose: 78 days (range: 30-180 days)	Median duration: 4.4 months (range: 1-10 months)	LGS patients: • Total seizure responder rate [†] : 38.5% • Median reduction in total seizures: 50%	LGS patients: • 11.5% experienced AEs • AEs: dizziness and lethargy (<i>n</i> =2), rash (<i>n</i> =1) • One patient discontinued due to AEs (dizziness and lethargy)
Thome-Souza <i>et al.</i> (Thome-Souza <i>et al.</i> , 2014)	Single-centre, retrospective chart review	300 patients with range of refractory epilepsies (mean age: 9.8 years; range: 0.4-29.6 years); 30 with LGS	Overall population: • Mean starting dose: 8.8 mg/kg/day (range: 0.9-52.6 mg/kg/day) • Mean final dose: 39.5 mg/kg/day (range: 1.8-135 mg/kg/day)	Median duration: 9 months (range: 1-37 months)	LGS patients: • Total seizure responder rate*: 63.3%	Overall population: • 26.3% experienced AEs • Most common AEs: sleepiness (26.6%), vomiting (21.5%), mood changes (16.5%), nausea (11.4%), and loss of appetite (11.4%) • All AEs were observed during initiation and titration period

Authors	Study design	Population	Rufinamide dosing	Follow-up	Key efficacy findings	Key tolerability findings
Kessler <i>et al.</i> (Kessler <i>et al.</i> , 2015)	Single-centre, retrospective cohort study	133 patients with range of epilepsy syndromes (median age: 10 years; range: 0.9-25.7 years); 39 with LGS (median age: 11.3 years; range: 2.1-23.5 years)	Overall population: • Median target dose: 33 mg/kg/day (range: 5-65 mg/kg/day) • Median maximum dose: 45 mg/kg/day (range: 5-105 mg/kg/day) • Median titration duration: 3 weeks (1-8 weeks)	Median duration of follow-up in LGS patients: 23 months (range: 9-30 months)	LGS patients: • Twice as likely to continue rufinamide without additional therapy vs. those without LGS ($p=0.007$) • Median time to rufinamide failure: 18 months vs. 6 months for those without LGS ($p=0.006$)	Overall population: • Most common AEs: gastrointestinal/loss of appetite (21.8%) and drowsiness (9.0%)
Korea						
Lee <i>et al.</i> (Lee <i>et al.</i> , 2013)	Single-centre, retrospective study	23 LGS patients (mean age: 11.4 years; range: 4-22 years)	Mean final dose: 35.1 mg/kg/day (range: 22.2-64.5 mg/kg/day)	Mean treatment duration: 8 months	• Retention rate: 78% after 6 months; 68% after 12 months • Total seizure responder rates* at 1, 3, and 6 months: 43.5%, 52.2%, and 40.9%, respectively	• 26.0% experienced AEs • AEs: somnolence ($n=3$), aggressive behaviour ($n=2$), and seizure aggravation ($n=1$) • Most AEs were transient and mild

Authors	Study design	Population	Rufinamide dosing	Follow-up	Key efficacy findings	Key tolerability findings
Kim <i>et al.</i> (Kim <i>et al.</i> , 2013)	Single-centre, retrospective study	53 children with refractory generalised epilepsy (median age: 7.9 years; range: 4.0-17.3 years); 20 with LGS	<ul style="list-style-type: none"> • Mean initial dose: 12.4 mg/kg/day (range: 5.6-23.5 mg/kg/day) • Mean maximum dose: 40.2 mg/kg/day (range: 6.7-83.3 mg/kg/day) 	<ul style="list-style-type: none"> • Mean follow-up duration: 9.9 months (range: 6-12 months) • Mean duration of rufinamide treatment: 7.6 months (range: 0.4-12 months) 	<p>LGS patients:</p> <ul style="list-style-type: none"> • Total seizure responder rate[†]: 40% at 3 months, 30% at 6 months • Seizure freedom rates: 20% at 3 months, 5% at 6 months <p>Overall population:</p> <ul style="list-style-type: none"> • Responder rate[†] at 6 months by seizure type: tonic-clonic, 60.0%; others (including absences and partial seizures), 53.3%; spasms, 33.3%; tonic, 29.0%; atonic, 27.3%; myoclonic, 21.1% • Seizure freedom rate at 6 months by seizure type: tonic-clonic, 20.0%; others (including absences and partial seizures); 13.3%; spasms, 11.1%; tonic, 9.7%; atonic, 9.1%; myoclonic, 5.3% 	<p>Overall population:</p> <ul style="list-style-type: none"> • 43.4% experienced AEs • Most common AEs: somnolence (<i>n</i>=8), poor appetite (<i>n</i>=5), and behavioural problems (<i>n</i>=3) • AEs leading to rufinamide discontinuation: behavioural problems (<i>n</i>=1), and rash (<i>n</i>=1) • Most AEs were transient and mild
Kim <i>et al.</i> (Kim <i>et al.</i> , 2012b)	Single-centre, retrospective, observational study	37 paediatric patients with intractable epilepsy (mean age: 10.5 years; range: 1.8-18.4 years); 10 with LGS	<ul style="list-style-type: none"> • Mean initial dose: 7.8 mg/kg/day (range: 2.6-31.5 mg/kg/day) • Mean final maintenance dose: 31.4 mg/kg/day (range: 6.1-65.6 mg/kg/day) 	<p>Mean treatment duration: 10.5 months</p>	<p>LGS patients:</p> <ul style="list-style-type: none"> • Total seizure responder rate*: 30% <p>Overall population:</p> <ul style="list-style-type: none"> • Total seizure responder rate*: 21.6% 	<p>Overall population:</p> <ul style="list-style-type: none"> • 27% experienced AEs • AEs: insomnia (<i>n</i>=3), loss of appetite (<i>n</i>=3), somnolence (<i>n</i>=2), irritability (<i>n</i>=2), vomiting (<i>n</i>=1), and dizziness (<i>n</i>=1) • Four patients discontinued rufinamide due to insomnia, vomiting, loss of appetite, and dizziness (<i>n</i>=1 for each)

*Response defined as $\geq 50\%$ seizure frequency reduction.

†Response defined as $> 50\%$ seizure frequency reduction.

AE: adverse event; GI: gastrointestinal; LGS: Lennox-Gastaut syndrome; VPA: valproate.

Of 30 patients who had tonic/atonic seizures and remained on treatment at 12 months, five (16.7%) became seizure-free and 17 (56.7%) were responders. There were statistically significant reductions in the frequency of generalised tonic-clonic seizures at six and 12 months ($p=0.001$ for both), tonic/atonic seizures at 12 months ($p=0.01$), and focal seizures at six months ($p=0.001$). After 12 months of rufinamide treatment, 28 patients (48.3%) were considered to be “much improved” or “very much improved” in terms of global impression of change. AEs were reported in 21 patients (36.2%), none of which were severe. The most commonly reported AEs were nausea, vomiting, and weight loss (Jaraba *et al.*, 2016).

An open, retrospective, multicentre, pragmatic study was conducted in eight Italian paediatric neurology clinics to assess the safety and efficacy of rufinamide add-on therapy in 40 children aged <4 years (mean age: 39.5 months) with a range of drug-resistant epilepsy syndromes, including four with LGS (Grosso *et al.*, 2014). The mean follow-up duration was 12.2 months and efficacy was assessed as seizure frequency reduction relative to baseline, according to seizure type and epilepsy syndrome. In the overall population, 11/40 (27.5%) patients were responders and two (5%) became seizure-free. In terms of seizure types, the highest seizure reduction rates were observed for epileptic spasms (46%) and drop attacks (42%), followed by tonic seizures (35%) and focal motor seizures (30%). In terms of epilepsy syndromes, two of the four LGS patients (50%) were responders, as were five of the 18 (27.8%) patients with focal epilepsy, one of whom became seizure-free. In addition, one of the four (25%) patients with West syndrome became seizure-free. AEs occurred in 15/40 (37.5%) patients overall and the most frequently reported AEs were vomiting (15%), drowsiness and nervousness (12.5%), and anorexia and weight loss (10%). Four patients discontinued treatment due to worsening seizure frequency and two due to AEs (vomiting and anorexia) (Grosso *et al.*, 2014).

The US experience

A single-centre, retrospective, observational, clinical practice study investigated the efficacy and safety of rufinamide treatment in patients with a variety of types of refractory epilepsy, including 26 patients with LGS (median age: 14 years; range: 4–21 years) (Vendrame *et al.*, 2010; Resnick *et al.*, 2011). Efficacy was assessed as seizure frequency on rufinamide treatment (median duration: 4.4 months), compared with the three months prior to starting rufinamide. The overall responder rate for the LGS patients was 38.5% and the median seizure frequency reduction was 50%. AEs were reported for three LGS patients (11.5%) and comprised dizziness and lethargy ($n=2$; leading to rufi-

namide discontinuation in one patient) and transitory rash ($n=1$) (Resnick *et al.*, 2011).

A single-centre, retrospective chart review assessed the retention, efficacy, and safety of rufinamide therapy in 300 patients (mean age: 9.8 years) with a wide range of refractory seizure types, over a median follow-up duration of nine months (Thome-Souza *et al.*, 2014). Seizure frequency at last follow-up visit was compared with the seizure frequency during the three months prior to initiating rufinamide. The study included 30 LGS patients, 19 of whom (63.3%) were responders. The authors commented that the relatively high responder rate observed in the study may reflect the exclusion of patients who had inefficiency and subsequent discontinuation within one month, and that changes in other medications and interventions (e.g. epilepsy surgery) may also have contributed to seizure reduction. Retention and safety were not specifically reported for LGS patients. In the overall population, rufinamide was discontinued in 36.7% of patients due to lack of efficacy and/or AEs. AEs were reported for 79/300 (26.3%) patients and the most frequently reported AEs ($\geq 10\%$ of patients) were sleepiness (26.6%), vomiting (21.5%), mood changes (16.5%), nausea (11.4%), and loss of appetite (11.4%). All AEs were observed during the initiation and titration period (Thome-Souza *et al.*, 2014). Another single-centre, retrospective cohort study assessed the retention of rufinamide therapy in 133 patients (median age: 10 years; range: 0.9–25.7 years) with a variety of epilepsy syndromes, 39 of whom (29.3%) had LGS (Kessler *et al.*, 2015). The median follow-up duration was 20 months in the overall population and 23 months in patients with LGS. The primary outcome measure was time to rufinamide failure, defined as discontinuation of rufinamide or initiation of an additional AED. Patients with LGS were twice as likely to continue rufinamide without additional therapy, compared with patients without LGS (unadjusted Cox proportional hazard ratio: 0.51; $p=0.007$). The median time to rufinamide failure was 18 months for LGS patients, compared with six months for patients without LGS ($p=0.006$). The probability of remaining on rufinamide at 12 months without additional therapy was 64% in patients with LGS versus 40% in those without LGS (35% vs. 30% at 24 months, respectively). Overall, the most common reason for rufinamide discontinuation was lack of efficacy ($n=43$; 32.3%). Safety was not specifically reported for LGS patients. In the overall population, the most commonly reported AEs ($\geq 5\%$ of patients) were gastrointestinal/loss of appetite (21.8%) and drowsiness (9.0%) (Kessler *et al.*, 2015).

The Korean experience

A single-centre, retrospective study assessed the efficacy and tolerability of rufinamide in 23 patients with

LGS (mean age: 11.4 years) (Lee *et al.*, 2013). The mean duration of rufinamide treatment was eight months and seizure frequency was assessed before starting rufinamide and one, three, and six months after starting rufinamide therapy. The retention rate was 78% after six months and 68% after 12 months. After one month, one patient (4.3%) achieved seizure freedom (which persisted over nine months of follow-up) and 43.5% of patients were responders. The responder rates after three and six months were 52.2% and 40.9%, respectively, and a reduction in seizure frequency of $\geq 50\%$ was maintained in 34.8% of patients after six months. Response to rufinamide was not significantly associated with age, sex, aetiology (symptomatic/cryptogenic), or duration of epilepsy. AEs were reported in 26.0% of patients and comprised somnolence ($n=3$), aggressive behaviour ($n=2$), and seizure aggravation ($n=1$). Most AEs were transient and mild (Lee *et al.*, 2013).

Another single-centre, retrospective study assessed the efficacy and tolerability of rufinamide in 53 children with refractory generalised epilepsy (median age: 7.9 years), including 20 children with LGS (Kim *et al.*, 2013). Efficacy was assessed as total monthly seizure frequency after three and six months. In the overall population, the mean duration of rufinamide treatment was 7.6 months. Among the LGS patients, the responder and seizure freedom rates were 40% and 20%, respectively, at three months, and 30% and 5%, respectively, at six months. Responder rates by seizure type among LGS patients were 66.7% (4/6) for atonic head drops, 60% (9/15) for tonic seizures, 33.3% (1/3) for tonic-clonic seizures, 25% (1/4) for spasms, and 16.7% (1/6) for myoclonic seizures. Two LGS patients discontinued rufinamide due to seizure aggravation. Overall, 43.4% (23/53) patients experienced 24 AEs; most commonly, somnolence ($n=8$), poor appetite ($n=5$), and behavioural problems ($n=3$). AEs leading to rufinamide discontinuation were behavioural problems ($n=1$) and rash ($n=1$). Most AEs were transient and mild (Kim *et al.*, 2013).

A third retrospective, observational study investigated the efficacy and tolerability of rufinamide in 37 paediatric patients (mean age: 10.5 years) with intractable epilepsy, including 10 patients with LGS, treated at a single epilepsy centre (Kim *et al.*, 2012b). Efficacy was assessed as responder rate. The mean duration of rufinamide therapy in the overall population was 10.5 months and rufinamide was discontinued in 46% (17/37) of patients after a mean duration of 5.6 months. The responder rate for the LGS patients was 30%, with 20% of patients experiencing $<50\%$ seizure frequency reduction and 50% experiencing unchanged seizure frequency. AEs were reported in 27% of the overall population and comprised insomnia ($n=3$), loss of appetite ($n=3$), somnolence ($n=2$), irritability ($n=2$),

vomiting ($n=1$), and dizziness ($n=1$). Four patients in the overall population discontinued rufinamide due to insomnia, vomiting, loss of appetite, and dizziness ($n=1$ for each) (Kim *et al.*, 2012b).

Rufinamide treatment for adults with LGS

Longitudinal studies have shown that by adulthood, approximately 50–75% of patients diagnosed with LGS during childhood no longer display all of the clinical and EEG features typically used to diagnose the syndrome and it can therefore be particularly difficult to recognise LGS in previously undiagnosed adult patients (Kerr *et al.*, 2011). Management of LGS in adulthood is also challenging, since seizures are often intractable and the majority of patients ($>90\%$) have moderate to severe cognitive impairment, which is frequently associated with behavioural difficulties, affecting social independence and occupational status (Kerr *et al.*, 2011). As in childhood, effective management of LGS in adulthood therefore requires a multidisciplinary and individualised approach to care that does not solely focus on seizure control (Kerr *et al.*, 2011).

In the original rufinamide Phase III trial (Glauser *et al.*, 2008), 31 adult LGS patients received adjunctive treatment with either rufinamide ($n=21$) or placebo ($n=10$) (McMurray and Striano, 2016). The mean age of patients was 25.2 (range: 18–35) and 29.3 (range: 18–37) years in the rufinamide and placebo groups, respectively, and the mean time since LGS diagnosis was 18.5 (range: 0–33) and 25.5 (range: 8–34) years, respectively. Following 12 weeks of double-blind treatment, the median percentage change from baseline in 28-day frequency of drop attacks was -54.9% for rufinamide, compared with $+21.7\%$ for placebo ($p=0.002$; figure 3A). Similarly, the median percentage change from baseline in 28-day frequency of total seizures was -31.5% for rufinamide versus $+22.1\%$ for placebo ($p=0.008$; figure 3A). Response was defined as $\geq 50\%$ seizure frequency reduction from baseline. Responder rates for drop attacks were 57.1% with rufinamide versus 10.0% with placebo ($p=0.020$) (figure 3B). Responder rates for total seizures were 33.3% with rufinamide versus 0% with placebo ($p=0.066$) (figure 3B). No patient achieved seizure freedom (*i.e.* freedom from all seizures), but two patients treated with rufinamide (9.5%) became free of drop attacks. In total, 15/21 (71.4%) patients treated with rufinamide and 6/10 (60.0%) patients treated with placebo experienced AEs. Consistent with the findings for the overall patient population in the original trial (Glauser *et al.*, 2008), the most frequently reported AEs (reported by $\geq 15\%$ of patients receiving

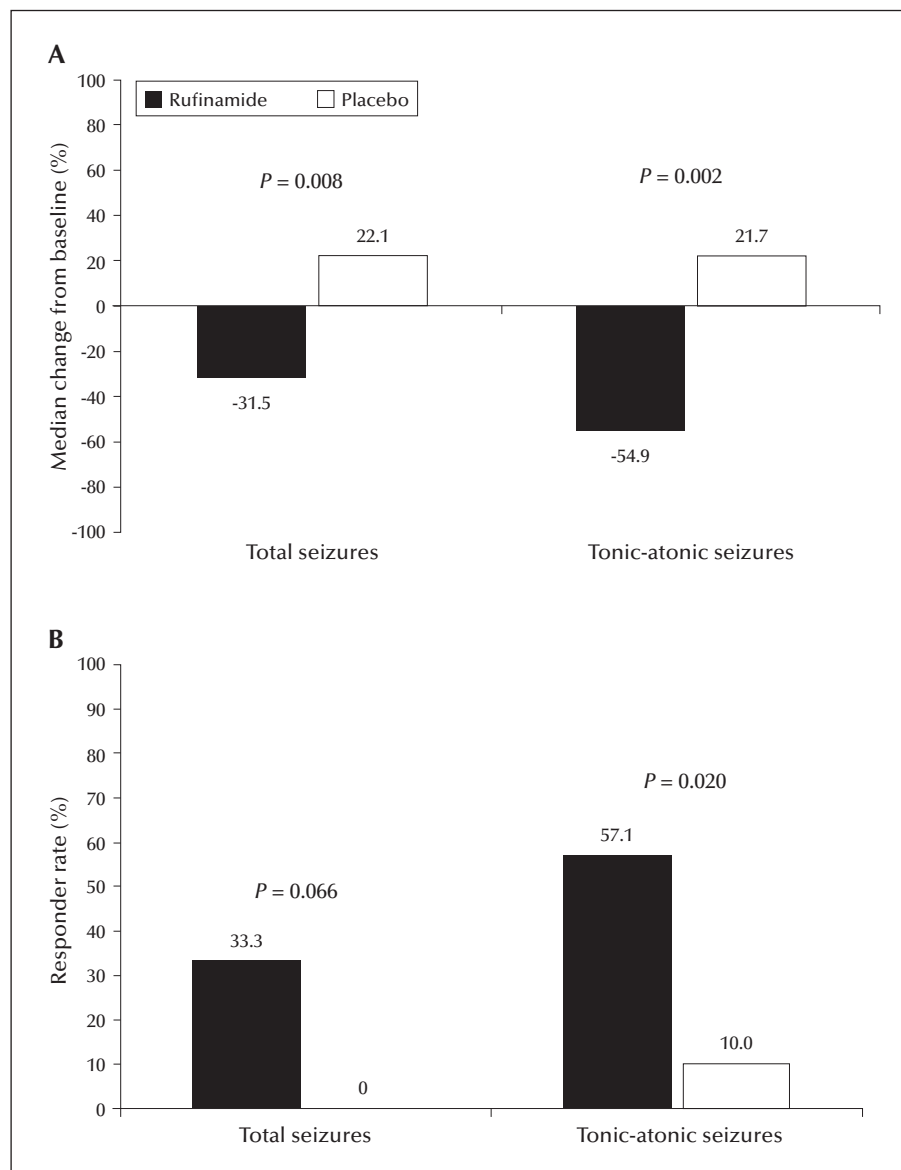


Figure 3. (A) Median percentage changes from baseline in 28-day frequency and (B) responder rates for all seizures and drop-attack seizures in adult patients with LGS ($n=31$). Response was defined as $\geq 50\%$ seizure frequency reduction from baseline. Adapted from McMurray and Striano, 2016.

rufinamide) were somnolence (33.3% with rufinamide vs. 20.0% with placebo) and vomiting (19.0% vs. 0%) (McMurray and Striano, 2016). The study therefore demonstrated that rufinamide was efficacious and generally well tolerated when used as an adjunctive treatment in adult patients with LGS. No new or unexpected safety concerns emerged in this patient subgroup (McMurray and Striano, 2016).

Weight loss is a common AE with rufinamide treatment (reported in more than one in 100 patients) (Inovelon® Summary of Product Characteristics, 2017). In a single-centre study conducted in France, clinically significant

weight loss (defined as $\geq 7\%$ decrease from baseline) was reported in seven of 15 consecutive adult patients treated with adjunctive rufinamide (age range: 18-31 years; mean age: 24.5 years) (Mourand *et al.*, 2013). Five of these seven patients had LGS. Overall, patients' body mass index decreased by 7.3-18.7%. Five of the seven patients with clinically significant weight loss were underweight before starting rufinamide therapy and four of these patients discontinued rufinamide because of weight loss. The authors suggested that a lower starting dose and slower titration rate might help minimise the possibility of weight loss, although

further research is required to confirm this (Mourand *et al.*, 2013).

In a thorough QT interval study, rufinamide treatment was shown to result in a decrease in corrected QT (QTc) interval that was proportional to its concentration, and clinicians are therefore advised to use their clinical judgment when assessing whether to prescribe rufinamide to patients at risk from further shortening of their QTc interval (Inovelon® Summary of Product Characteristics, 2017). In a single-centre study conducted in Germany, the mean QT interval of 19 consecutive adult patients treated with adjunctive rufinamide (age range: 21–68 years; mean age: 41 years), nine of whom had LGS, shortened significantly with rufinamide treatment; mean QT intervals were 349 ms (QTc interval: 402 ms) before initiation of rufinamide and 327 ms (QTc interval: 382 ms) after achieving steady state ($p=0.002$) (Schimpf *et al.*, 2012). The mean (standard deviation) reduction in the QTc interval was -20 (18) ms. However, during a mean follow-up of 3.6 years, no symptomatic cardiac arrhythmias occurred and no AEs, such as syncope and sudden unexpected death in epilepsy, were reported (Schimpf *et al.*, 2012).

Discussion

Rufinamide was initially granted orphan drug status and its approval was based on the results of a single Phase III trial conducted in 138 patients (Glauser *et al.*, 2008). It was therefore important to assess whether the efficacy and safety/tolerability of rufinamide observed in this trial are consistent with other clinical trials and maintained over the longer term. In addition, since clinical trials are conducted using set protocols in carefully selected patient populations, it was important to assess how rufinamide's efficacy and safety/tolerability in the clinical trial setting translate into effectiveness in clinical practice, where patients are more diverse than those recruited into clinical trials (e.g. in terms of age, comorbidities, and comedications), and treatment is individualised on a patient-by-patient basis, rather than according to a set schedule. Longer-term surveillance is also required in order to monitor for the potential emergence of AEs that are either rare or take an extended time to appear.

Taken as whole, evidence from clinical trials, supported by data from clinical practice studies, has confirmed that rufinamide is effective as an adjunctive treatment for seizures associated with LGS. Rufinamide has been shown to be effective in children as young as one year of age and in adults. Importantly, rufinamide is particularly effective in treating seizures that mostly affect patients' quality of life; namely, drop attacks (tonic-atonic seizures) and generalised tonic-clonic seizures. Rufinamide is generally

well tolerated as an adjunctive therapy for LGS, and the most common side effects include somnolence, headache, dizziness, nausea, vomiting, and fatigue. No new or unexpected safety signals have emerged following long-term treatment, either in clinical trials or in clinical practice.

Clinical practice studies further complement evidence from clinical trials by providing practical information on how a drug is used in the real-world setting; for example, in terms of dosing and titration. In the initial Phase III trial, rufinamide was titrated according to a recommended schedule and the target dose (approximately 45 mg/kg/day) was achieved by 88% of rufinamide-treated patients (Glauser *et al.*, 2008). Titration took place over a maximum of 14 days, the majority of rufinamide-treated patients who achieved the target dose (77%) doing so in approximately seven days (Glauser *et al.*, 2008). Rufinamide dosing in clinical practice appears to be somewhat lower than that used in clinical trials, with up-titration conducted over a longer time period. For example, in the Kluger *et al.* study conducted in Germany and Austria, the mean maintenance dose was 34 mg/kg/day and this was generally achieved within approximately four weeks (Resnick *et al.*, 2011; Kluger *et al.*, 2009); in the Auvin *et al.* study conducted in France, the mean initiation dose was approximately 3 mg/kg/day, the mean maintenance dose was 8 mg/kg/day, and the mean titration period was approximately 13 weeks (Auvin *et al.*, 2014a; Auvin *et al.*, 2014b). Lower dosing and/or longer titration does not appear to affect rufinamide's efficacy, but may result in improvements in tolerability; in the Phase III trial, 81% of patients treated with rufinamide experienced AEs (Glauser *et al.*, 2008), whereas the overall incidence of AEs reported for LGS patients in clinical practice studies, where stated, ranged from 12 to 52% (table 2).

Clinical practice studies have therefore provided additional insights into the effectiveness of rufinamide and ways in which its effectiveness may be optimised in everyday practice. However, additional questions relating to its use require further clarification. These include whether specific drug combinations with rufinamide are particularly effective and/or well tolerated as treatment for LGS, and whether combining rufinamide with an agent with a similar mechanism of action could potentially increase the likelihood of AEs. Other questions requiring further research include whether patients who do not show an initial response to rufinamide may benefit from an increased dose, if tolerated, and how early in the disease course of LGS rufinamide should be considered.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF



(1) What are the three features that are commonly thought to characterise Lennox-Gastaut syndrome?

(2) Which seizure type, commonly associated with Lennox-Gastaut syndrome, is rufinamide considered to be particularly effective in treating?

(3) Which of the following is not one of the most common side effects of rufinamide treatment?

- A. Somnolence
- B. Weight increase
- C. Fatigue

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".