Epilepsy & Behavior 46 (2015) 221–226

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clobazam is equally safe and efficacious for seizures associated with Lennox–Gastaut syndrome across different age groups: Post hoc analyses of short- and long-term clinical trial results

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ARTICLE INFO

Article history:
Received 18 December 2014
Revised 26 January 2015
Accepted 28 January 2015
Available online 1 May 2015

Keywords:
Clobazam
Lennox–Gastaut syndrome
Drop seizures
Total seizures
Age groups
Post hoc analyses

ABSTRACT

The peak age at onset of Lennox–Gastaut syndrome (LGS) is between 3 and 5 years. Patients with LGS frequently experience multiple types of treatment-refractory seizures and require lifelong therapy with several antiepileptic drugs. Here, post hoc analyses of clinical trials (phase III trial OV-1012 and open-label extension trial OV-1004) provide short- and long-term efficacy and safety data of adjunctive clobazam in patients with LGS stratified by age at baseline (≥2 to <12 years, ≥12 to <17 years, and ≥17 years). In OV-1012, 301 patients were screened, 238 were randomized, 217 comprised the modified intention-to-treat population, and 177 completed the study. A total of 267/306 patients (61 of 68 from phase II trial OV-1002 and 206 of 238 from phase III trial OV-1012) entered the open-label extension trial. Demographics and clinical characteristics were similar between different age groups in OV-1012 and OV-1004. No differences in efficacy or adverse events were observed across age groups in OV-1012 and OV-1004. The results of these post hoc analyses show that adjunctive clobazam over the short and longterm was similarly effective and well-tolerated in both pediatric and adult patients with LGS.

1. Introduction

Lennox–Gastaut syndrome (LGS) is a severe type of epilepsy that has a peak age at onset between 3 and 5 years [1,2]. Patients with LGS typically experience multiple seizure types, predominantly tonic and atonic seizures that can cause the patient to suddenly fall ("drop seizures"). These patients often have seizures that are refractory to treatment with antiepileptic drugs (AEDs), and many require lifelong AED polytherapy to manage their multiple seizure types [1,3–6]. As patients with LGS age and transition from pediatric to adult care, it is clinically important to understand the efficacy and safety of AEDs across the age spectrum [7].

Approved by the U.S. Food and Drug Administration (FDA) in October 2011, the 1,5-benzodiazepine clobazam is indicated for the adjunctive treatment of seizures associated with LGS in patients 2 years and older. The results from two randomized controlled studies (phase II OV-1002 [NCT00162981] [8] and phase III OV-1012 [NCT00518713], also known as the CONTAIN trial [9]) demonstrated that clobazam was efficacious and well-tolerated for the treatment of LGS. Patients from the lead-in studies were eligible to enroll in OV-1004 (NCT01160770), an open-label extension (OLE) trial [10]. The results from the up to 6-year OLE study showed that stable dosages of adjunctive clobazam improved seizure control, with some patients achieving and maintaining long-term seizure freedom.

To evaluate short- and long-term clobazam efficacy and safety across different ages, we conducted post hoc analyses of patient data grouped by those who were ≥2 to <12 years, ≥12 to <17 years, and ≥17 years of age at baseline.

2. Materials and methods

Data for these post hoc analyses were derived from both the phase III trial OV-1012 (short-term results) [9] and OLE trial OV-1004 (long-term results) [10]. Detailed methodologies for both studies have been published and are summarized below.

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http://dx.doi.org/10.1016/j.yebeh.2015.01.037

Table 1
OV-1012 (A) and OV-1004 (B) patient demographics and baseline characteristics by age groups (safety populations).

A) OV-1012

	≥2 to <12 years (children)		≥12 to <17 years (adolescents)		≥17 years (adults)	
	Placebo (N = 36)	Clobazam (N = 110)	Placebo (N = 10)	Clobazam (N = 30)	Placebo (N = 13)	Clobazam (N = 39)
Age, years						
Mean (SD)	7.7 (2.58)	6.8 (2.83)	14.2 (1.36)	14.2 (1.49)	26.6 (10.09)	26.1 (7.70)
Median	7.4	7.1	14.4	13.9	24.1	24.1
Male, n (%)	21 (58.3)	66 (60.0)	8 (80.0)	16 (53.3)	9 (69.2)	24 (61.5)
Weekly drop-seizure rate at baseline						
Mean (SD)	108.1 (150.94)	95.2 (154.96)	141.1 (287.56)	113.5 (241.27)	25.8 (28.71)	26.7 (30.51)
Median	57.3	39.5	25.5	21.3	9.3	18.4
Range	2–744	2–994	6–920	3–1077	3–87	2–170
Time since LGS diagnosis, years						
Mean (SD)	2.9 (2.69)	2.7 (2.85)	8.9 (3.45)	7.9 (3.21)	22.2 (10.96)	21.5 (8.33)
Prior number of AEDs, n (%)						
0	3 (8.3)	7 (6.4)	0	1 (3.3)	0	1 (2.6)
1	3 (8.3)	25 (22.7)	2 (20.0)	5 (16.7)	1 (7.7)	5 (12.8)
2	7 (19.4)	17 (15.5)	2 (20.0)	3 (10.0)	0	3 (7.7)
3	4 (11.1)	12 (10.9)	0	3 (10.0)	1 (7.7)	4 (10.3)
≥4	19 (52.8)	49 (44.5)	6 (60.0)	18 (60.0)	11 (84.6)	26 (66.7)

B) OV-1004

	Children (N = 176)	Adolescents (N = 45)	Adults (N = 46)
Age, years			
Mean (SD)	7.0 (2.65)	14.1 (1.48)	24.6 (8.32)
Median	7.2	13.9	22.0
Male, n (%)	109 (61.9)	28 (62.2)	26 (56.5)
Time since LGS diagnosis, years			
Mean (SD)	2.7 (2.47)	7.6 (3.55)	19.4 (9.44)
Prior number of AEDs, n (%)			
0	10 (5.7)	1 (2.2)	0
1	20 (11.4)	5 (11.1)	5 (10.9)
2	22 (12.5)	6 (13.3)	2 (4.3)
3	17 (9.7)	3 (6.7)	3 (6.5)
≥4	107 (60.8)	30 (66.7)	36 (78.3)

2.1. Studies OV-1012 and OV-1004

Trial OV-1012 was a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients eligible to participate in this trial were between 2 and 60 years of age with a diagnosis of LGS (onset at <11 years of age), weighing ≥12.5 kg, and receiving stable dosages of 1 to 3 AEDs (except benzodiazepines) for ≥30 days. A 4-week baseline period, a 3-week titration period, and a 12-week maintenance period comprised the study. During the baseline period, patients who experienced ≥2 drop seizures were stratified by weight (12.5 kg to ≤30 kg and >30 kg) and then randomized to 1 of 3 clobazam treatment groups (low-dosage clobazam: target of 0.25 mg/kg/day [maximum: 10 mg/day], medium-dosage clobazam: target of 0.5 mg/kg/day [maximum: 20 mg/day], and high-dosage clobazam: target of 1.0 mg/kg/day [maximum: 40 mg/day]) or placebo.

Open-label extension trial OV-1004 enrolled patients who participated in the phase II study OV-1002 [8] or the phase III study OV-1012 [9]. Most patients initially received 0.5 mg/kg/day (≤20 mg/day) of open-label clobazam. Dosages were then adjusted based on clinical response (efficacy and tolerability), up to a maximum of 2.0 mg/kg/day (80 mg/day); the published mean maximum dosage for Years 3 through 5 was 1.2 mg/kg/day [10]. Patients outside the United States did not continue in the study beyond 24 months (per protocol), resulting in much lower patient numbers for Year 3 and beyond, independent of efficacy and safety results.

2.2. Post hoc analyses of efficacy and safety

Patient efficacy and safety data from studies OV-1012 and OV-1004 were evaluated by the following age groups at baseline: ≥2 to <12 years (children), ≥12 to <17 years (adolescents), and ≥17 years (adults).

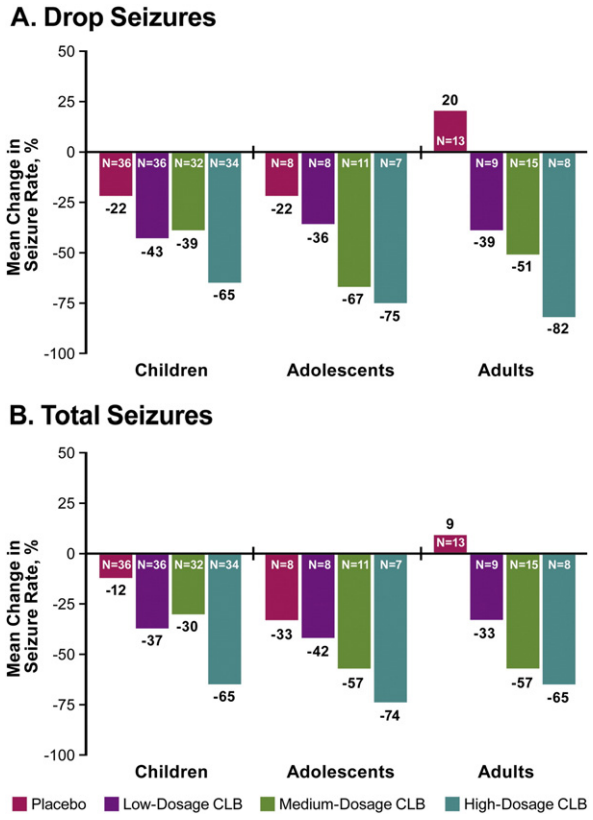

Fig. 1. Percentage decreases in average weekly rate of drop (A) and total (B) seizures by age in OV-1012: children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years). CLB, clobazam.

Efficacy outcomes for trial OV-1012 included the mean percentage decrease in weekly drop- and total-seizure (drop and nondrop) frequency and treatment responders by mean weekly rates (≥50% and 100%) of drop and total seizures during the maintenance vs. baseline phases for the modified intention-to-treat (mITT) population. For study OV-1004, efficacy outcomes included the median percentage decrease in the average weekly rate of drop and total seizures and responder rates for reduction from baseline (≥50% and 100%) in average weekly rate of drop and total seizures evaluated from baseline to Years 1 through 3.

Safety outcomes included adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, and clinical and laboratory findings. Safety data for the overall trial populations have been published [9,10].

2.3. Statistical analyses

The safety population included all patients who received treatment during either trial. For the OV-1012 analyses, the mITT population included all randomized patients who had baseline data, ≥1 dose of study medication, and ≥1 daily seizure measurement during the maintenance phase. In OLE study OV-1004, the efficacy analysis set included all patients with baseline and postbaseline assessments within the designated year. For the OLE trial, baseline was defined as 1) the last week of recorded seizures prior to receiving their first dose of clobazam for patients who received placebo in OV-1012 or 2) the last week of recorded seizures from the baseline period of the blinded study for patients who received clobazam in OV-1002 or OV-1012.

3. Results

3.1. Patient demographics and baseline clinical characteristics

In OV-1012, 301 patients were screened and 238 were randomized. Of these, 217 patients comprised the mITT population, and 177 completed the study [9]. The safety population included 146 children, 40 adolescents, and 52 adult patients. A total of 267 of 306 eligible patients from the lead-in trials (OV-1002: 61/68 patients; OV-1012: 206/308 patients) entered, and 188 (70%) completed OLE study OV-1004. A total of 251 patients had received clobazam for ≥6 months, 229 for ≥1 year, 210 for ≥2 years, 121 for ≥3 years, 54 for ≥4 years, and 44 for ≥5 years [10]. Of the 89 patients who discontinued between Years 2 and 3, 39 were outside the United States and were discontinued per protocol. The safety population included 176 children, 45 adolescents, and 46 adult patients. Demographic and baseline characteristics data for patients in trials OV-1012 and OV-1004 are presented in Table 1.

3.2. Efficacy by age groups

Percentage decreases in drop and total seizures in OV-1012 were similar across age groups and proportional to clobazam dosage in both

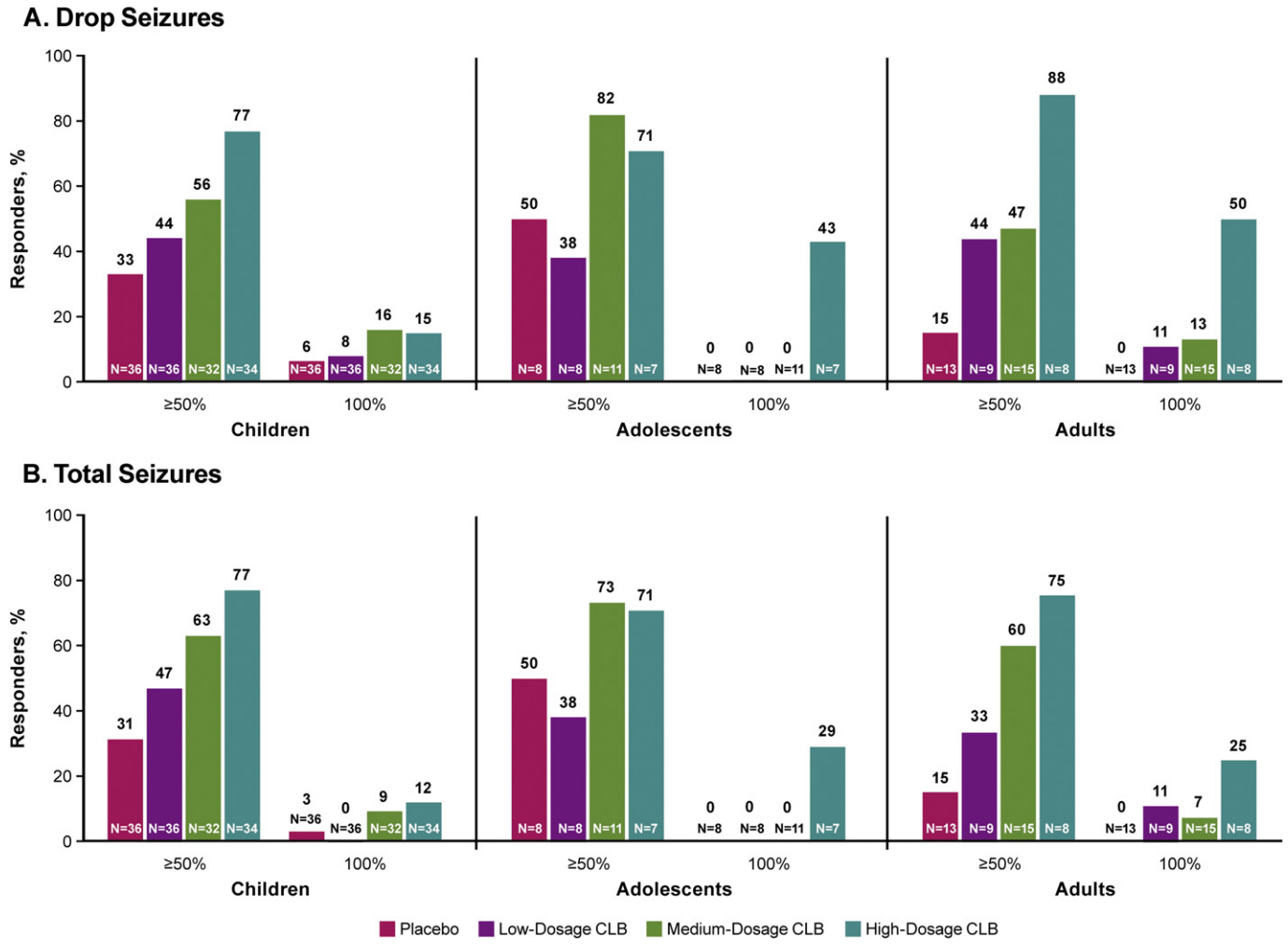

Fig. 2. ≥50% and 100% responders by average weekly rate of drop (A) and total (B) seizures by age group in OV-1012: children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years). CLB, clobazam.

adolescent and adult patients (Fig. 1). Responder rates (≥50% and 100%) for drop and total seizures by age groups are presented in Fig. 2. Treatment with medium- and high-dosage clobazam resulted in numerically ≥50% responder rates than placebo across all age groups.

In the OLE trial, the median seizure decreases were substantial and sustained in all age groups (Fig. 3). Data for patients who were ≥50% responders or experienced seizure freedom (100% responders) across the age groups are presented in Fig. 4. The percentages of patients who experienced a ≥50% response rate and seizure freedom were sustained for drop and total seizures through Year 3 across all age groups.

3.3. Safety by age group

Adverse events that occurred at ≥10% of clobazam-treated patients across age groups in OV-1012 are presented in Table 2. A total of 13/110 (12%) and 1/39 (3%) clobazam-treated children and adults, respectively, experienced an SAE; no adolescent patients experienced an SAE. A total of 10/110 (9%) clobazam-treated children vs. 1/36 (3%) placebo-treated children, 7/30 (23%) vs. 0/10 (0%) adolescents, and 8/39 (21%) vs. 1/13 (8%) adults experienced an AE that led to discontinuation from the trial.

In the OLE trial, a similar percentage of patients in each age group experienced AEs (children: 163/176 [93%], adolescents: 41/45 [91%], and adult patients: 42/46 [91%]) (Table 3). The incidence rates of SAEs were 42% for children, 42% for adolescents, and 48% for adults. A total of 11 (6%) children and 7 (15%) adults discontinued the OLE trial because of AEs, of which none occurred in >2 patients.

Six children died during the OLE trial. Fatal AEs were pneumonia (3 patients), cardiopulmonary arrest (1 patient), the combination of preexisting seizure increase, atelectasis, and hypoxic respiratory failure (1 patient), and death of unknown etiology (1 patient). One adolescent patient died because of pneumonia. A total of three adults died (1 patient each because of epilepsy; the combination of pneumonia, acute respiratory distress syndrome [ARDS], and sepsis; and ARDS and right leg hematoma). The AE of convulsion with an outcome of death in one child was considered "possibly related" to clobazam by the investigator; all other deaths were deemed "unlikely related" or "not related" to clobazam.

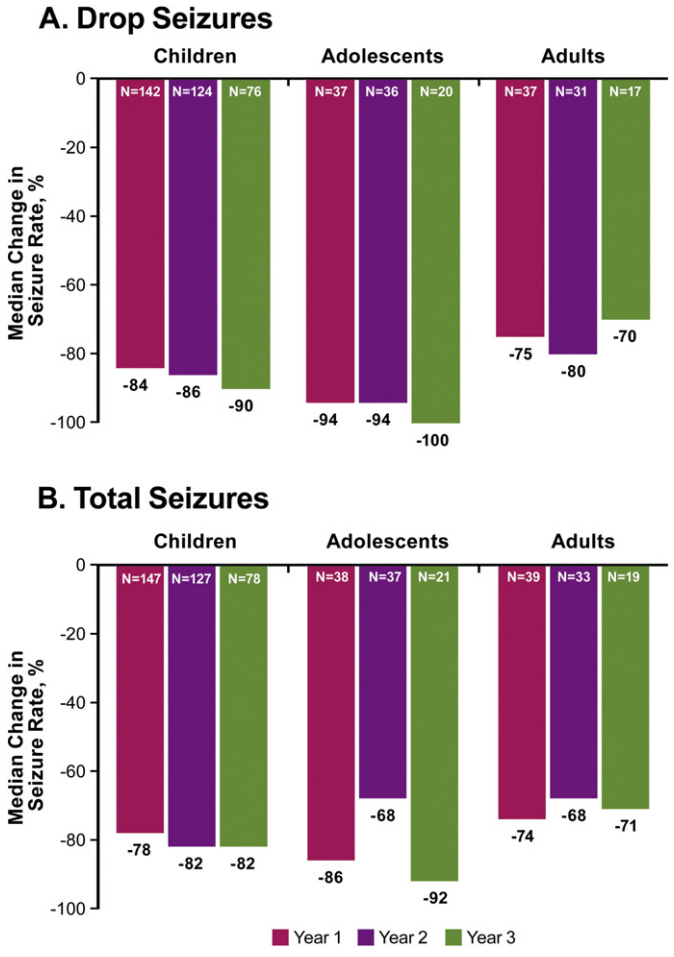

Fig. 3. Percentage decreases in average weekly rate of drop (A) and total (B) seizures by age group in OV-1004 (OLE): children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years).

4. Discussion

These post hoc analyses of the double-blind and OLE trials evaluated the short- and long-term efficacy and safety of clobazam in children, adolescents, and adults with a diagnosis of LGS (before 11 years of age).

Analyses of short-term efficacy data from the double-blind trial showed that clobazam-treated patients achieved similar percentages of drop- and total-seizure decreases across age groups. Drop- and total-seizure responder rates were consistent across age groups, especially for patients in the medium- and high-dosage clobazam treatment groups. A greater percentage of adolescent and adult patients who received high-dosage clobazam appear to achieve notable rates of drop- and total-seizure freedom. Evaluation of long-term efficacy data from the OLE trial showed that median drop- and total-seizure decreases as well as ≥50% and 100% drop- and total-seizure responder rates were sustained across age groups through Year 3. These data indicate that adult patients treated with clobazam responded nearly as well as children, despite presumably having a longer duration of seizure disorder. Though these short- and long-term efficacy results are informative, they are only descriptive. Furthermore, the limited number of adolescent and adult patients prevents substantive statistical analyses of these data. Finally, although patients from the long-term trial could have discontinued the study because of lack of efficacy, only 6% had elected to withdraw, which suggests limited patient enrichment for efficacy [10].

Safety analyses of the short- and long-term trial data across the age groups were consistent with the overall safety results [9,10]. Pyrexia occurred more frequently in pediatric patients (<17 years), which is to be expected, whereas aggression, ataxia, and drooling occurred more frequently in adolescent and adult patients. Serious AEs were more frequently reported in children, of which pneumonia and lobar pneumonia were most common, yet not unexpected. Pediatric patients discontinued from OV-1012 for lethargy and somnolence, whereas adult patients discontinued for aggression, ataxia, and insomnia. In the OLE trial, AEs such as pyrexia, pneumonia, and otitis media were more commonly reported in children; however, for a trial of this duration, these AEs were anticipated. The incidences of commonly reported SAEs were similar across age groups, and no noticeable difference was observed regarding AEs that led to discontinuation. Overall, these data suggest that clobazam had a similar tolerability profile for patients with LGS across age groups.

Although the onset of LGS often occurs in patients between 3 and 5 years of age, unfortunately, most patients do not outgrow their epileptic encephalopathy even if their EEG characteristics change over time. Most patients experience lifelong treatment-resistant epilepsy and intellectual disabilities, and many have behavioral issues such as aggression [7,11]. These post hoc analyses show that adults with LGS experienced similar drop- and total-seizure responses following treatment with clobazam as younger patients. These findings suggest that clobazam remains an appropriate treatment option across all age groups.

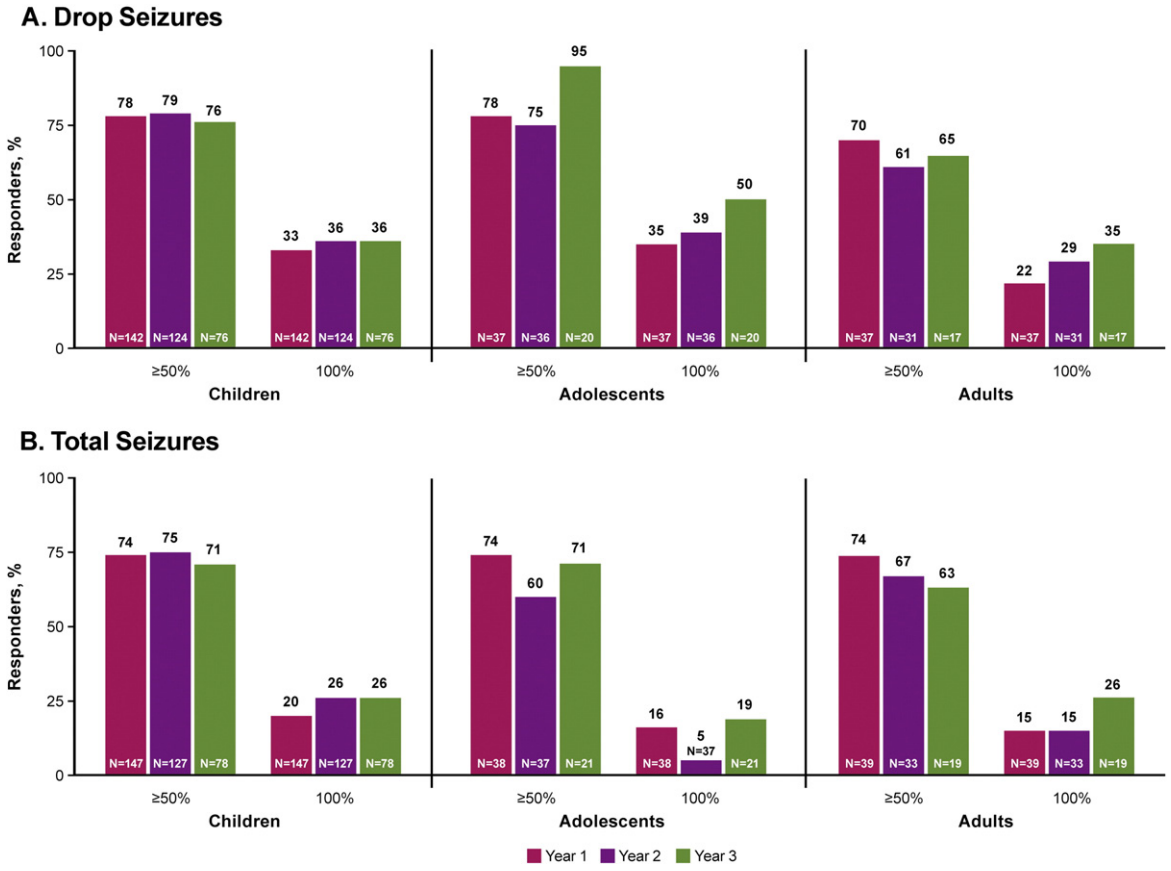

Fig. 4. ≥50% and 100% responders by average weekly rate of drop (A) and total (B) seizures by age group in OV-1004 (OLE): children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years).

Conclusions

Efficacy data analyses from trials OV-1012 [9] and OV-1004 [10] of patients with LGS treated with adjunctive clobazam demonstrated similar and sustained efficacy results over the short and long-term in children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years). Short- and long-term analyses of safety data did not reveal unexpected trends by age group. The results of these post hoc analyses show that adjunctive clobazam was equally effective and well-tolerated across the age spectrum.

Acknowledgments

Manuscript preparation, including editing and formatting the manuscript, incorporating author comments, preparing tables and figures, and coordinating submission requirements, was provided by Apurva Davé, PhD, of Prescott Medical Communications Group (Chicago, IL). This editorial support was funded by Lundbeck LLC.

Disclosures and conflicts of interest

This study was funded by Lundbeck LLC (Deerfield, IL). Drs. Isojarvi, Drummond, and Lee are Lundbeck employees.

Dr. Ng is on the speakers' bureaus for Eisai Inc., Lundbeck LLC, Supernus Pharmaceuticals, Inc., and UCB Inc. and has served on scientific advisory boards for Eisai Inc., Lundbeck LLC, Questcor Inc., and Upsher-Smith Laboratories Inc. Dr. Ng is an Associate Editor for *Pediatric Neurology*.

Dr. Conry is a principal investigator for clinical trials sponsored by Ovation Pharmaceuticals Inc. (acquired by Lundbeck LLC), Pfizer Inc.,

Table 2
OV-1012: adverse events reported by ≥10% of clobazam-treated patients: (A) ≥2 to <12 years (children), (B) ≥12 to <17 years (adolescents), and (C) ≥17 years (adults) (safety population).

A) Children		
AE	Placebo (N = 36), n (%)	Clobazam (N = 110), n (%)
Any AE	21 (58.3)	88 (80.0)
Somnolence	6 (16.7)	24 (21.8)
URTI	4 (11.1)	21 (19.1)
Pyrexia	2 (5.6)	18 (16.4)
B) Adolescents		
AE	Placebo (N = 10), n (%)	Clobazam (N = 30), n (%)
Any AE	8 (80.0)	22 (73.3)
Lethargy	0	7 (23.3)
Somnolence	0	7 (23.3)
Aggression	1 (10.0)	3 (10.0)
Ataxia	0	3 (10.0)
Drooling	0	3 (10.0)
Nasopharyngitis	3 (30.0)	3 (10.0)
Pyrexia	0	3 (10.0)
C) Adults		
AE	Placebo (N = 13), n (%)	Clobazam (N = 39), n (%)
Any AE	11 (84.6)	32 (82.1)
Somnolence	1 (7.7)	8 (20.5)
Aggression	2 (15.4)	7 (17.9)
Fatigue	1 (7.7)	5 (12.8)
Sedation	1 (7.7)	5 (12.8)
Ataxia	1 (7.7)	4 (10.3)
Drooling	0	4 (10.3)
Insomnia	0	4 (10.3)
Psychomotor hyperactivity	1 (7.7)	4 (10.3)

AE, adverse event; URTI, upper respiratory tract infection.

Table 3
OV-1004: adverse events reported by ≥10% of total patients (safety population).

AE	≥2 to <12 years (children) (N = 176), n (%)	≥12 to <17 years (adolescents) (N = 45), n (%)	≥17 years (adults) (N = 46), n (%)	Total (N = 267), n (%)
Any AE	163 (92.6)	41 (91.1)	42 (91.3)	246 (92.1)
URTI	53 (30.1)	12 (26.7)	10 (21.7)	75 (28.1)
Pyrexia	41 (23.3)	8 (17.8)	4 (8.7)	53 (19.9)
Pneumonia	36 (20.5)	8 (17.8)	2 (4.3)	46 (17.2)
Somnolence	32 (18.2)	5 (11.1)	9 (19.6)	46 (17.2)
Fall	23 (13.1)	9 (20.0)	13 (28.3)	45 (16.9)
Otitis media	37 (21.0)	4 (8.9)	1 (2.2)	42 (15.7)
UTI	21 (11.9)	7 (15.6)	11 (23.9)	39 (14.6)
Constipation	23 (13.1)	7 (15.6)	7 (15.2)	37 (13.9)
Convulsion	19 (10.8)	8 (17.8)	5 (10.9)	32 (12.0)
Sinusitis	23 (13.1)	2 (4.4)	7 (15.2)	32 (12.0)
Insomnia	23 (13.1)	5 (11.1)	3 (6.5)	31 (11.6)
Nasopharyngitis	17 (9.7)	10 (22.2)	4 (8.7)	31 (11.6)
Viral infection	13 (7.4)	8 (17.8)	7 (15.2)	28 (10.5)
Lethargy	12 (6.8)	6 (13.3)	9 (19.6)	27 (10.1)

AE, adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Marinus Pharmaceuticals Inc., and King Pharmaceuticals Inc. and is a consultant for Lundbeck LLC.

Dr. Mitchell has received or currently receives research support from Lundbeck LLC, Pfizer Inc., and UCB Inc.

Dr. Buchhalter has served as a consultant to Eisai Inc., UCB Inc., and Upsher-Smith Laboratories, Inc.

Dr. Chung has received research support from Eisai Inc., Lundbeck LLC, Medtronics, Inc., SK Life Science Inc., UCB Inc., and Upsher-Smith Laboratories Inc. and has served on scientific advisory boards or speakers' bureaus for Acorda Therapeutics, Eisai Inc., Lundbeck LLC, SK Life Science Inc., Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals Inc., UCB Inc., and Upsher-Smith Laboratories Inc.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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