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# 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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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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**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).

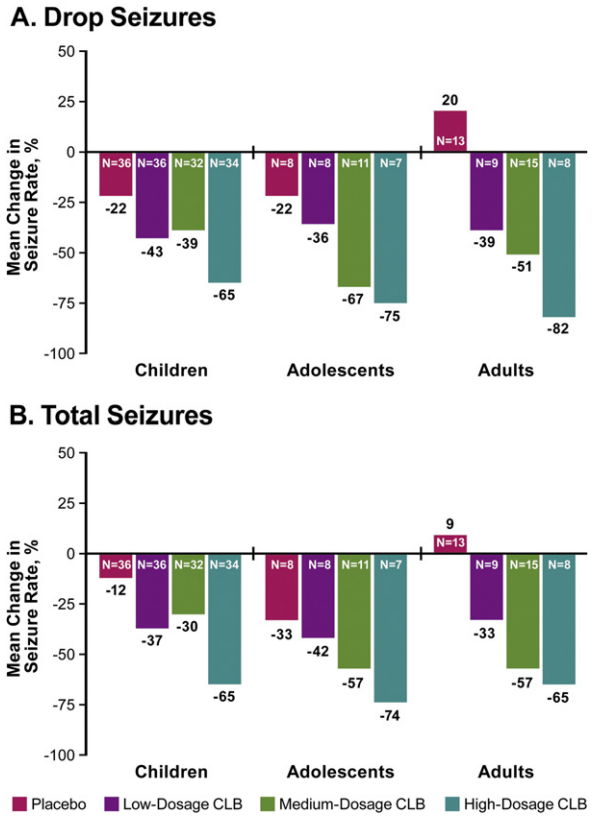


**Fig. 1.** Percentage decreases in average weekly rate of drop (A) and total (B) seizures by age in OV-1012: children (≥2 to <12 years), adolescents (≥12 to <17 years), and adults (≥17 years). CLB, clobazam.