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# Clobazam is efficacious for patients across the spectrum of disease severity of Lennox–Gastaut syndrome: Post hoc analyses of clinical trial results by baseline seizure-frequency quartiles and VNS experience

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ABSTRACT

Lennox–Gastaut syndrome (LGS) severity varies considerably, so the potential impact of differences in baseline severity on patient outcome following treatment is clinically informative. Here, two surrogate indicators of LGS severity (baseline seizure frequency and vagus nerve stimulation [VNS] use) were used in post hoc analyses of both short- and long-term clobazam trials (Phase III OV-1012 [CONTAIN] and open-label extension [OLE] OV-1004). In CONTAIN, 217 patients comprised the modified, intention-to-treat population. Each baseline seizure-frequency quartile had ~40 patients, and baseline weekly drop-seizure frequency ranges were as follows: <10 (Quartile 1), 10–30 (Quartile 2), 32–86 (Quartile 3), and 86–1077 (Quartile 4). Mean percentage decreases in average weekly drop and total seizures were similar for all quartiles. More than 50% of patients in all 4 quartiles demonstrated ≥50% decreases in weekly drop- and total-seizure frequency. The percentage of patients achieving 100% reduction in drop seizures was 33% for clobazam-treated patients (vs. 7% for placebo) in Quartile 1. Five percent of clobazam-treated patients in Quartile 4 (most severe LGS) vs. 0% for placebo achieved 100% reduction in drop seizures. A total of 267 of 306 possible patients entered the OLE (61/68 from a Phase II study and 206/238 from Phase III CONTAIN). Each quartile had ~66 patients, and baseline weekly drop-seizure ranges were as follows: <10 (Quartile 1), 10–31 (Quartile 2), 32–110 (Quartile 3), and 111–1147 (Quartile 4). Median percentage decreases in average weekly drop and total seizures were similar between quartiles. Through 5 years of therapy, >50% of patients in all 4 quartiles demonstrated ≥50% decreases in weekly frequency for drop seizures. More than 12% of patients in Quartile 4 achieved 100% reduction in drop seizures from Month 3 through Year 5. For the VNS analyses in CONTAIN, the least-squares mean decreases in average weekly rate of drop seizures (mITT population) were 52% for VNS patients receiving clobazam vs. −22% for placebo ($p < 0.01$). For non-VNS patients, these percentages were 53% for clobazam and 26% for placebo ($p < 0.01$). Moreover, 50% and 54% of clobazam-treated patients in the VNS and non-VNS groups demonstrated ≥50% decreases in average weekly drop- and total-seizure frequencies, and 11% and 14% in the two groups achieved drop-seizure freedom, respectively. Analyses using baseline seizure frequency and VNS use as surrogates for disease severity showed that clobazam treatment of patients with less severe or severe LGS was equally efficacious.



## 1. Introduction

Lennox–Gastaut syndrome (LGS) is a severe form of childhood epilepsy with no known cure [1,2]. The peak age at onset of LGS is between 3 and 5 years, and patients typically experience multiple seizure types. The most common are tonic and atonic seizures, and both can cause the patient to suddenly fall ("drop seizures") and sustain injury [3,4]. Patients with LGS often have seizures refractory to treatment with antiepileptic drugs (AEDs) and require chronic AED polytherapy to manage their multiple seizure types [1,5,6]. Given that LGS severity varies considerably, it is clinically important to understand an AED's effect in patients across the LGS spectrum.

Clobazam, a 1,5-benzodiazepine, was approved by the U.S. Food and Drug Administration (FDA) in October 2011 for the adjunctive treatment of seizures associated with LGS in patients 2 years and older. Clobazam was shown to be efficacious and well-tolerated for the treatment of LGS in two randomized controlled studies (Phase II OV-1002 [NCT00162981] [7] and Phase III OV-1012, also known as the CONTAIN trial [NCT00518713] [8]). After participation in these studies, patients were eligible to enroll in an open-label extension (OLE) trial [OV-1004 (NCT01160770)]. The results from this 6-year study showed

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that stable dosages of adjunctive clobazam improved seizure control, with some patients achieving and maintaining seizure freedom over the long term [9].

To evaluate both short- and long-term clobazam efficacy across the LGS severity spectrum, we conducted post hoc analyses of patient data grouped by 1) baseline seizure frequency in CONTAIN and the OLE or 2) vagus nerve stimulation (VNS) use in CONTAIN.

## 2. Materials and methods

Data for these post hoc analyses were derived from the CONTAIN trial [8] and the OLE [9,10]. Detailed methodologies for both studies have been published and are summarized in the following subsections.

### 2.1. Studies OV-1012 (CONTAIN) and OV-1004 (open-label extension trial)

CONTAIN was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study [8]. Patients 2 to 60 years of age with a diagnosis of LGS (onset at <11 years of age), weighing ≥12.5 kg, and currently receiving stable dosages of 1 to 3 AEDs (except benzodiazepines) for ≥30 days were eligible to participate. The study included a 4-week baseline period, a 3-week titration period, and a 12-week maintenance period (Fig. 1). Patients who experienced ≥2 drop seizures during the baseline period 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.

Study OV-1004 was an OLE trial that enrolled patients who completed the 7-week, Phase II OV-1002 study [7] or the 15-week, Phase III CONTAIN study [8] (Fig. 1) [9]. Most patients initially received 0.5 mg/kg/day (≤40 mg/day) of open-label clobazam. Dosages were then adjusted based on clinical response (efficacy and tolerability), up to 2.0 mg/kg/day (80 mg/day). Per protocol, patients outside the United States did not continue in the study beyond 24 months, resulting in much lower patient numbers for Year 3 and beyond, independent of efficacy and safety results.

### 2.2. Post hoc analyses: determination of LGS severity at baseline

Baseline seizure frequency was used as a surrogate indicator of disease severity in patients enrolled in the CONTAIN and OLE studies. Patients were grouped by quartile based on their average baseline weekly drop and total (drop and nondrop) seizure frequencies. These groups were designed to have an approximately equal distribution of patients per quartile per trial by seizure type.

Additional analyses of patient data from the CONTAIN trial used VNS status as an indicator of disease severity. Any VNS use during the trial qualified patients for grouping with the "VNS group," which was considered more severe than the "non-VNS group."

### 2.3. Statistical analyses

For the CONTAIN trial analyses, a modified intention-to-treat (mITT) population (defined as all randomized patients who received ≥1 dose of the study drug, had baseline data, and had ≥1 daily seizure measurement during the 12-week maintenance period) was

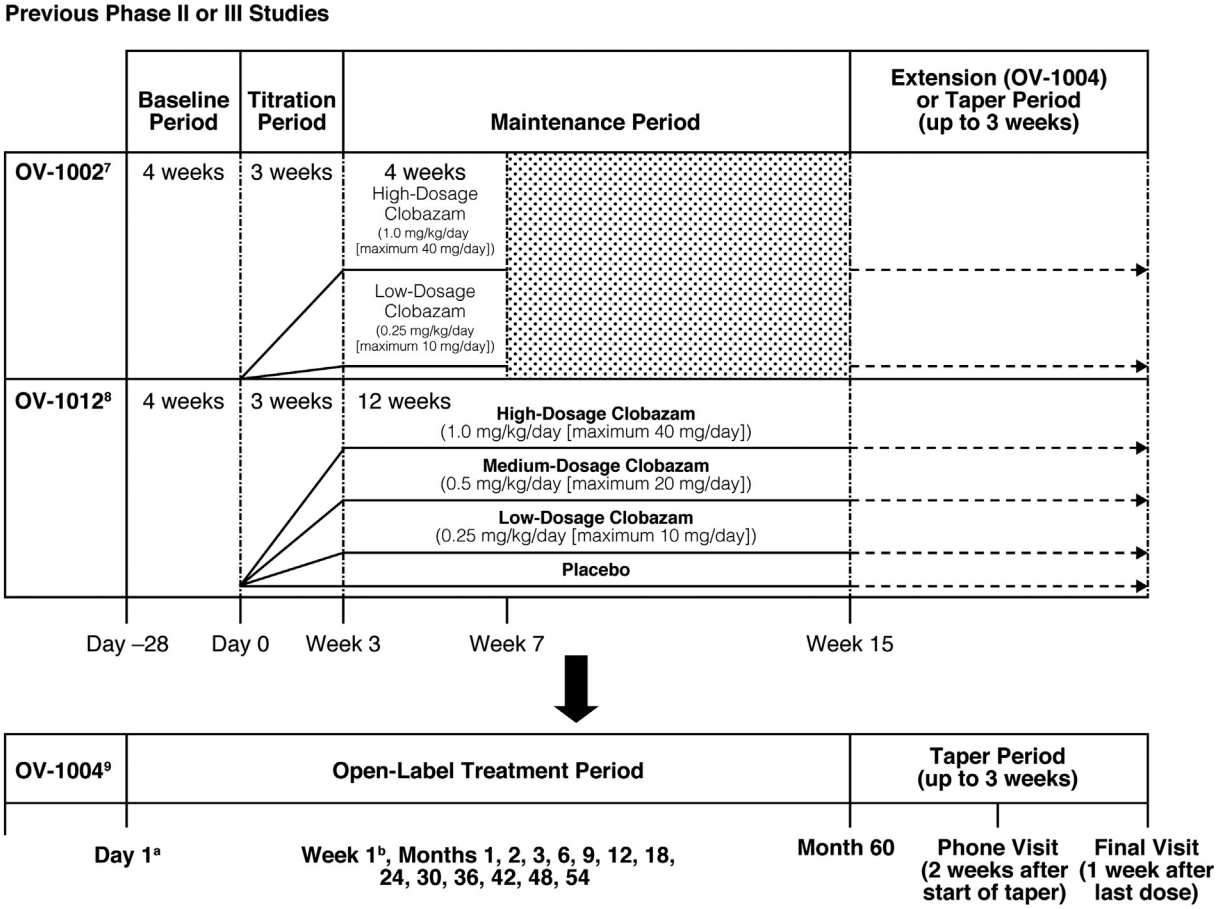


**Fig. 1.** OV-1012 (CONTAIN) and OV-1004 (open-label extension) study designs. [a]End of a previous blinded study and the start of the open-label study. [b]Week 1 visit only applied to patients who participated in OV-1012 (patients in OV-1002 had passed the Week 1 time point prior to the amendment change that added Week 1 procedures).
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