Received: 24 July 2020 | Revised: 26 March 2021 | Accepted: 11 April 2021

DOI: 10.1002/epi4.12492

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Pregabalin as adjunctive therapy in adult and pediatric patients with generalized tonic-clonic seizures: A randomized, placebo-controlled trial

Joseph Driscoll[1] | Mary Almas[2] | Gabriela Gregorian[1] | Alla Kyrychenko[3] | Iryna Makedonska[4] | Jing Liu[1] | Jeffrey Patrick[1] | Joseph M. Scavone[1]* | Jeremias Antinew[1] | on behalf of the 1105 Study Group

[1]Pfizer Inc, Groton, CT, USA

[2]Pfizer Inc, New York, NY, USA

[3]Department of Internal Medicine, Dnipro Medical Institute of Conventional and Alternative Medicine, Dnipro, Ukraine

[4]Dnipro City Children's Clinical Hospital #5 of Dnipro City Council, Dnipro, Ukraine

Correspondence
Joseph Driscoll, Clinical Director, Pfizer Inc, Eastern Point Rd, Bldg 260, Groton, CT 06340, USA.
Email: joseph.driscoll@pfizer.com

Funding information
Study A0081105 was sponsored by Pfizer.

Abstract

Objective: Generalized tonic-clonic (GTC) seizures are the most common type of generalized seizure and more common in children than adults. This phase 3 study evaluated the efficacy and safety of pregabalin for GTC seizures in adults and children with epilepsy.

Methods: This randomized, double-blind, multicenter study evaluated pregabalin (5 mg/kg/day or 10 mg/kg/day) vs placebo as adjunctive therapy for 10 weeks (following a 2-week dose escalation), in pediatric and adult patients (aged 5-65 years) with GTC seizures. Primary endpoint was change in log-transformed 28-day seizure rate during active treatment. Secondary endpoints included responder rates, defined as proportion of patients with ≥50% reduction in 28-day GTC seizure rate from baseline. Safety was monitored throughout.

Results: Of 219 patients, 75, 72, and 72 were randomized to adjunctive pregabalin 5 mg/kg/day, 10 mg/kg/day, and placebo, respectively. Fifteen, 11, and 6 patients discontinued from the 5 mg/kg/day, 10 mg/kg/day, and placebo arms, respectively, most commonly due to adverse events (AEs; 10.7%, 6.9%, and 5.6%, respectively). A nonsignificant change in log-transformed mean 28-day seizure rate was seen with pregabalin 10 mg/kg/day vs placebo (least-squares [LS] mean difference –0.01 [95% confidence interval (CI) –0.19 to 0.16]; P = .8889) and with pregabalin 5 mg/kg/day vs placebo (LS mean difference 0.02 [CI –0.15 to 0.19]; P = .8121). Similar observations were noted for adults and children. No significant differences were seen for secondary endpoints with pregabalin vs placebo, including responder rate. The most common AEs (≥10%) were dizziness, headache, and somnolence. Most were of mild/moderate intensity. Seven patients had serious AEs, with one death in the placebo arm (sudden unexpected death in epilepsy).

ClinicalTrials.gov identifier: NCT01747915.

*At time of study conduct.

Significance: Adjunctive pregabalin treatment did not change GTC seizure rate in adults or children. The safety profile of pregabalin was similar to that known; treatment was well tolerated with few discontinuations due to AEs.

KEYWORDS
antiepileptic drug, epilepsy, generalized tonic-clonic seizures, pregabalin

1 | INTRODUCTION

Epilepsy is a collective term for different seizure types that may have a differential response to treatment strategies. With approximately 50 million people estimated worldwide to have epilepsy in 2019,[1] epilepsy is one of the most common neurological diseases. The global incidence rate of epilepsy in 2017 was estimated to be 61.44 per 100 000 person-years,[2] although the incidence has two peaks: reportedly higher in the first year of life and in those aged ≥85 years.[3] Primary generalized tonic-clonic (PGTC) seizures, formerly "grand mal" seizures, are the most common type of generalized seizure,[4] occurring in approximately 20% of patients, and more common in children than adults.[4] While PGTC was the terminology in use when the present study initiated (according to International League Against Epilepsy [ILAE] 2010 criteria)[5], the shorter "generalized tonic-clonic (GTC) seizures" are used to categorize these seizures following the updated ILEA terminology in 2017.[6] For consistency with updated terminology, we use this throughout rather than PGTC. Childhood epilepsy in particular is defined by a wide spectrum of clinical manifestations,[7] and diagnosis is challenging and carries high risk for misdiagnosis.[8,9] The impact of childhood epilepsy pediatric patients and their families is considerable, highlighting the need for ongoing research into management strategies.[8]

First- and subsequent-generation antiepileptic drugs (AEDs) are available for the management of different types of seizures in patients with epilepsy,[7,10-12] and guidelines provide recommendations for treatment selection, with criteria for selection of newer second- or third-generation AEDs, which may have superior safety profiles compared to first-generation AEDs.[10,13,14] Despite available AEDs, approximately one-third of patients have inadequate seizure control, and evidence suggests rates of control in newly diagnosed epilepsy have not improved over the past 30 years.[15,16] The majority of patients who attain seizure control across epilepsy subtypes do so with the first or second AED.[16]

Pregabalin is an alpha-2-delta ligand, approved in certain countries as adjunctive therapy for partial-onset seizures in adults and pediatric patients from 1 month or older.[17] Efficacy data have demonstrated that pregabalin reduces seizure frequency in patients with focal-onset seizures (FOS)[18-24] (according to ILAE 2017 terminology, FOS will be used throughout[4]). For example, a ≥50% reduction in seizure frequency was observed in 43%–51% of adults receiving pregabalin 600 mg/day[20-22,24] and 41% of pediatric patients (aged 4-16 years) receiving pregabalin 10 mg/kg/day.[18] The efficacy of pregabalin has not been assessed as adjunctive therapy in patients with GTC seizures. This study sought to evaluate the efficacy and safety of pregabalin for the management of GTC seizures in adult and pediatric patients with epilepsy. The study was carried out as part of a postmarketing commitment to the US Food and Drug Administration (FDA).

Key Point

- Generalized tonic-clonic (GTC) seizures are the most common type of generalized seizure and more common in children than adults.
- This study evaluated pregabalin (5 mg/kg/day or 10 mg/kg/day) vs placebo as adjunctive therapy in pediatric and adult patients with GTC seizures.
- No significant change in 28-day seizure rate was seen with either dose of pregabalin vs placebo.
- Most AEs were mild or moderate; the most common AEs were dizziness, headache, and somnolence.

2 | METHODS

2.1 | Study design

This randomized, double-blind, placebo-controlled, parallel group, phase 3 study of pregabalin was approved and conducted in 21 countries (Austria, Belarus, Bosnia and Herzegovina, Bulgaria, China, France, Greece, Hungary, India, Malaysia, Montenegro, Poland, Romania, Russian Federation, Serbia, Slovakia, South Korea, Turkey, Ukraine, UK, and United States). A full list of participating centers and investigators is given in Table S1. The first patient first visit was on April 3, 2013, and last patient last visit February

20, 2019. The study is registered under the ClinicalTrials.gov identifier: NCT01747915.

The study had four phases: an 8-week baseline phase, 12-week double-blind assessment phase, comprising a 2-week double-blind dose escalation and 10-week fixed-dose phases, and 1-week double-blind taper phase (Figure S1). Data from the taper phase were not used in the efficacy analysis. Ten clinic visits took place over the study period.

2.2 | Patient populations

Eligible patients were 5-65 years, with a diagnosis of epilepsy with PGTC seizures according to ILAE 2010 guidelines[25] (termed GTC throughout in line with 2017 update of ILEA terminology[6]). Randomization was stratified by site and age-group (5-7 years, 8-11 years, 12-16 years, 17-65 years), with an aim to enroll ~30% in pediatric groups (5-17 years). Every reasonable effort was made to enroll ≥12 subject per age-group. Prior to randomization, a sponsored, appointed, independent central reviewer (The Epilepsy Consortium, New York, NY, USA) confirmed each patient met diagnostic eligibility and had a diagnosis of idiopathic generalized epilepsy. Eligible patients had ≥1 GTC seizure in the 8 weeks prior to screening, ≥3 GTC seizures during 8-week baseline phase, and ≥1 GTC seizure in each 4-week period of the baseline phase. Eligible patients also received adequate and stable doses of 1-3 AEDs, and were stabilized within 28 days of screening. Patients (or their guardians) received instructions on how to maintain a diary to record seizures (including seizure type). Study investigators reviewed diaries with patients or their guardians to help ensure correct recording and understanding of classification of seizures.

Patients with a current diagnosis of febrile seizures or seizures related to an ongoing medical illness were excluded. Patients with FOS, status epilepticus (within 1 year of screening), Lennox-Gastaut syndrome, infantile spasms, benign epilepsy with centrotemporal spikes, Dravet syndrome, or seizures related to drugs, alcohol, or acute medical illness were not eligible.

The study was conducted in accordance with the Declaration of Helsinki. The final protocol, including any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each participating study center. Informed consent was obtained from patients or their guardians prior to entering the study.

2.3 | Treatment schedule

During the baseline phase, patients maintained their current AED regimen. Following screening and eligibility assessment, patients were randomized using a telerandomization system to receive (1:1:1 ratio) pregabalin (5 mg/kg/day [maximum 300 mg/day], pregabalin 10 mg/kg/day [maximum 600 mg/day]), or placebo for 12 weeks. For pediatric patients weighing <30 kg, daily dose of pregabalin (administered in liquid form) was increased by 40%, from 5 to 7 mg/kg/day or 10 to 14 mg/kg/day, depending on assigned arm, to ensure they achieved similar pregabalin exposure to adults, according to the prescribing label.[26] Dose selection was based on US and EU recommendations for pregabalin in FOS patients.[17,27] Pregabalin or placebo treatments were administered orally, twice-daily (BID) in capsule or liquid formulation, with capsules preferred for patients who could ingest them.

2.4 | Efficacy and safety endpoints

The primary endpoint was log-transformed ($\log_e$) 28-day GTC seizure rate during the 12-week double-blind assessment phase and did not include seizure data recorded during the taper phase. The 28-day GTC seizure rate was calculated as:

$$28\text{-day seizure rate} = \frac{\#\text{ of seizures in the double-blind assessment phase of study}}{\left[\#\text{ of days in period} - \#\text{ of missing diary days in period}\right]} \times 28$$

When log-transformation was used, "1" was added to the 28-day seizure rate to account for any "0" seizure incidence, giving: $\log_e$ seizure rate = (28-day seizure rate +1).

Secondary efficacy endpoint was responder rate, defined as patients achieving ≥50% reduction in 28-day seizure rate during the 12-week double-blind assessment phase, as measured from baseline (data collected during 8-week baseline phase). Patients not achieving a 50% reduction were defined as nonresponders. Exploratory endpoints included (a) proportion of seizure-free days, overall and for each seizure type (GTC seizures, myoclonic, tonic/atonic, absence, clonic seizures), defined as (# seizure-free days in a given period)/(# days in a period – # missing seizure diary days); (b) adjusted number of seizure-free days gained per 12-weeks, defined as (# seizure-free days in given period x 84)/(# days in the period – # missing days in period); and (c) proportion of GTC seizure freedom over double-blind assessment phase (patients received ≥84 days of fixed-dose treatment).

Safety was monitored by recording treatment-emergent adverse events (AEs). Mandatory, predetermined seizure exit criteria were episode of status epilepticus during assessment phase and 28-day GTC seizure rate during assessment phase that was greater than twice the maximum seizure rate during the baseline phase; potential seizure exit criteria were episode of a newly

emergent seizure type or an increase in GTC or other generalized seizure activity deemed significant by the investigator. Suicidal ideation was captured and behavior assessments recorded, as required, using the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), the eight-item Patient Health Questionnaire depression scale (PHQ-8), and the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaires at screening and C-SSRS throughout the study. Mental health risk assessments were carried out if any patient met necessary criteria based on these questionnaires. Body weight, clinical laboratory data, physical and neurological examinations, and electrocardiograms were also captured.

2.5 | Statistical analysis

A total of 168 patients were planned to be enrolled to provide ≥80% power to detect a significant difference in the primary endpoint ($\log_e$ 28-day seizure rate) between pregabalin 10 mg/kg/day and placebo, and pregabalin 5 mg/kg/day and placebo (with pregabalin dose adjusted by weight, as required), assuming a difference in $\log_e$ 28-day seizure rate between pregabalin 600 mg and placebo of –0.534 (translating to percent difference of −41.4%) and a difference between pregabalin 300 mg and placebo of –0.358 (translating to percent difference of −30.1%), with a common standard deviation of 0.67 (translating to percent scale of common standard deviation of 95.4). Expected difference was 80% of the observed difference between specified pregabalin dose minus placebo based on a meta-analysis of three previous studies (Study 1008-009[22], 1008-011[21], 1008-034[24]; data on file).

Efficacy analyses were performed on the intent-to-treat population, comprising all randomized patients who took ≥1 dose of pregabalin or placebo during the assessment phase, had a baseline value, and ≥1 postbaseline efficacy assessment (seizure diary entry). The safety set included all randomized patients who took ≥1 dose of pregabalin or placebo. AEs are reported using descriptive statistics (eg, counts and percentages). The primary efficacy analysis was performed on $\log_e$ 28-day GTC seizure rate (28-day seizure rate +1), using a linear model with ordinary least-squares (LS), with treatment, age stratum, and geographic region as fixed factors and $\log_e$ (baseline seizure rate +1) as continuous covariate. A sequential stepwise testing procedure was used to control for multiplicity such that the experimentwise type I error rate would not exceed 5% level. Step 1 tested the null hypothesis of equal treatment group means (μ) of pregabalin (PGB) 10 mg/kg/day vs placebo (PBO) at $\alpha = 0.05$ two-sided for the primary endpoint (H01: μPGB 10 – μPBO = 0; Ha1: μPGB 10 – μPBO ≠ 0). Step 2 was tested only when H01 was rejected. Step 2 tested the null hypothesis of equal treatment group means (μ) of pregabalin 5 mg/kg/day vs placebo at $\alpha = 0.05$ two-sided for the primary endpoint (H02: μPGB 5 – μPBO = 0; Ha2: μPGB 5 – μPBO ≠ 0). Missing values for seizures were handled by subtracting the number of missing diary days from the denominator of 28-day seizure rate equation. Each dose of pregabalin and placebo was compared in a pairwise manner using a sequential stepwise testing procedure. Two-sided 95% confidence intervals (CIs) of the difference between LS means were calculated using the appropriate LS means and their standard errors.

Results were also reported as percentage reduction in seizures relative to placebo. Percentage reduction was calculated by backwards transformation of seizure log (exponentiation of log seizure rate) by 100%*(exp(X)–1), where X is the difference in LS mean of seizure rate in log scale between each dose of pregabalin and placebo.

Responder rates were analyzed using a logistic regression model with fixed covariate terms for treatment group, weight, and geographic region. Comparisons were performed for each pregabalin dose vs placebo using maximum likelihood tests and 95% CIs. Each dose of pregabalin and placebo was compared using a sequential stepwise testing procedure. Treatment group comparisons were summarized with odds ratios of achieving responder status.

3 | RESULTS

3.1 | Patient demographics and disposition

A total of 219 patients were randomized to pregabalin 5 mg/kg/day (n = 75) or pregabalin 10 mg/kg/day (n = 72), or placebo (n = 72). As noted, this was a postmarketing safety commitment to the FDA with a requirement to enroll ≥12 patients in each age-group. Enrollment of adults outpaced pediatric patients, leading to overenrollment. Overall, 153 adult and 66 pediatric patients were enrolled; thus, the stipulation for enrolling ~30% across pediatric age-groups was met. Most frequent reasons for discontinuation were treatment-emergent AEs (n = 14 [6.4%]) and no longer willing to participate (n = 9 [4.1%]; Figure 1). Discontinuation due to prespecified seizure exit criteria was recorded as AE or as other. Eight (3.7%) patients met ≥1 predetermined seizure exit criteria: 1 (1.3%) on pregabalin 5 mg/kg/day and 3 (4.2%) on placebo had 28-day GTC seizure rate during the double-blind assessment phase that was greater than twice the baseline rate; 1 patient (1.3%) on pregabalin 5 mg/kg/day had an episode of status epilepticus; 3 patients (4.0%) on pregabalin 5 mg/kg/day (including 1 with increasing numbers of absence seizures as adjudicated by the investigator), 1 patient (1.3%) on pregabalin 10 mg/kg/day, and 1 (1.3%) on placebo had clinically significant increases in seizure frequency or

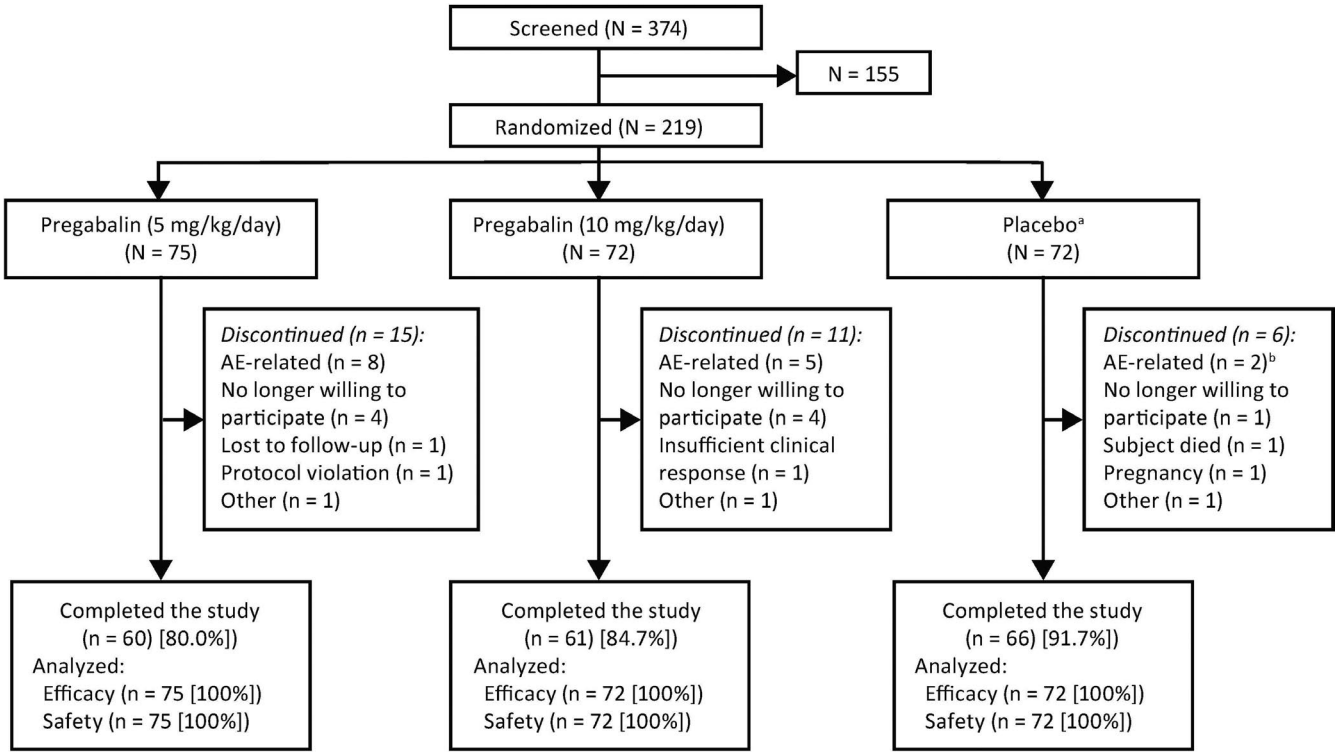

FIGURE 1 Flow of patients through the study. [a]Patients continued their AED regimen. [b]AE-related withdrawals were all considered related to the study drug, with the exception of one patient in the placebo arm (where the AE was considered not to be study drug–related). AE, adverse event and AED, antiepileptic drug

intensity. While 2 patients discontinued treatment due to an increase in frequency of myoclonic seizures (1 in each pregabalin 5 mg/kg/day and 10 mg/kg/day groups, respectively), these patients did not meet predetermined seizure exit criteria.

All patients were taking 1-3 AEDs, with 42.0%, 45.2%, and 12.8% taking 1, 2, and 3 AEDs, respectively (Table 1). The most frequent AEDs taken prior to the study, and concomitantly during the study, were levetiracetam, valproic acid/valproate sodium, and lamotrigine. Valproic acid was the most common AED taken prior to the study and concomitantly by patients 5-16 years (40.9%) and levetiracetam for patients aged 17-65 years (35.3%).

Mean duration since GTC onset was 14.8 years (range: 0.1-57.8 years). In total, 42.5% of patients had a history of generalized absence seizures and 24.7% a history of generalized myoclonic seizures (Table 1). In line with exclusion criteria, no subjects had a history of generalized clonic, tonic, atonic, or tonic/atonic seizures, or history of partial-onset seizures, status epilepticus, or unclassified epileptic seizures. Treatment compliance was high (≥98.2%) in each treatment arm, overall and regardless of age-group. Mean dose during the fixed-dose phase with pregabalin 5 mg/kg/day group was 256 mg/day (204 mg/day for pediatric patients; 286 mg/day for adults). In 10 mg/kg/day group, mean dose was 535 mg/day (453 mg/day for pediatric patients; 575 mg/day in adults).

3.2 | Change in $\log_e$ 28-day seizure rate (primary efficacy analysis)

The baseline mean $\log_e$ 28-day seizure rate was similar across treatment groups (Figure 2). A nonsignificant reduction in mean $\log_e$ 28-day seizure rate was seen with pregabalin 10 mg/kg/day vs placebo (LS mean difference –0.01 [95% CI –0.19 to 0.16]; P =.8889). Since the pregabalin 10 mg/kg/day group did not reach significance, the primary endpoint analysis for pregabalin 5 mg/kg/day group vs placebo was nonsignificant per the prespecified sequential stepwise testing procedure (LS mean difference 0.02 [95% CI –0.15 to 0.19]; P =.8121). There was no significant difference when treatment by age-group interaction was assessed (P =.5340), suggesting that $\log_e$ 28-day GTC seizure rate was homogenous across age-groups (5-16 years old and 17-65 years old). Results from the sensitivity analyses were consistent with the outcomes of the primary endpoint analyses. In addition, there was no significant difference in the percentage reduction vs placebo in 28-day seizure rate with either pregabalin 10 mg/kg/day (–1.8%) or pregabalin 5 mg/kg/day (3.1%).

3.3 | Change in mean 28-day seizure rate

Mean 28-day seizure rates at baseline were 6.1, 3.3, and 3.6 in pregabalin 5 mg/kg/day, pregabalin 10 mg/kg/day, and placebo

TABLE 1 Baseline characteristics, overall and by age category (safety set)

	Pregabalin 5 mg/kg/day	Pregabalin 10 mg/kg/day	Placebo	Total
All patients	**n = 75**	**n = 72**	**n = 72**	**N = 219**
Age, years (mean ± SD)[a]	24.0 ± 13.3	25.4 ± 12.7	26.2 ± 13.2	25.2 ± 13.1
5-7, mean (%)	6 (8.0)	5 (6.9)	6 (8.3)	17 (7.8)
8-11, mean (%)	7 (9.3)	7 (9.7)	5 (6.9)	19 (8.7)
12-16, mean (%)	13 (17.3)	10 (13.9)	7 (9.7)	30 (13.7)
17-65, mean (%)	49 (65.3)	50 (69.4)	54 (75.0)	153 (69.9)
Male (n, %)	33 (44.0)	33 (45.8)	32 (44.4)	98 (44.7)
Weight, kg (mean ± SD)	63.3 ± 25.3	63.7 ± 20.3	63.3 ± 21.8	63.5 ± 22.5
Height, cm (mean ± SD)	161.2 ± 20.1	162.5 ± 16.7	162.0 ± 19.1	161.9 ± 18.6
Mean duration since GTC onset, years (range)	14.6 (0.6-57.8)	13.8 (0.1-44.6)	15.9 (0.5-54.9)	14.8 (0.1-57.8)
History of generalized absence seizures[a], %	36.0	50.0	41.7	42.5
History of generalized myoclonic seizures[a], %	70.7	73.6	81.9	75.3
Number of concomitant AEDs, n (%)				
1	30 (40.0)	32 (44.4)	30 (41.7)	92 (42.0)
2	33 (44.0)	32 (44.4)	34 (47.2)	99 (45.2)
3	12 (16.0)	8 (11.1)	8 (11.1)	28 (12.8)
Type of AEDs, n (%)				
Levetiracetam	24 (32.0)	24 (33.3)	24 (33.3)	72 (32.9)
Valproic acid	18 (24.0)	17 (23.6)	21 (29.2)	56 (25.6)
Lamotrigine	15 (20.0)	18 (25.0)	16 (22.2)	49 (22.4)
Topiramate	13 (17.3)	10 (13.9)	10 (13.9)	33 (15.1)
Aged 5-16 years[b]	**n = 26**	**n = 22**	**n = 18**	**N = 66**
Age, years (mean ± SD)	10.3 ± 3.4	10.9 ± 3.4	9.8 ± 3.5	10.4 ± 3.4
Male (n, %)	12 (46.2)	14 (63.6)	9 (50.0)	35 (53.0)
Race, n (%)				
White	22 (84.6)	20 (90.9)	17 (94.4)	59 (89.4)
Asian	4 (15.4)	2 (9.1)	1 (5.6)	7 (10.6)
Weight, kg (mean ± SD)	40.6 ± 20.1	44.8 ± 20.9	32.5 ± 11.3	39.8 ± 18.8
Height, cm (mean ± SD)	143.8 ± 20.1	147.2 ± 16.7	137.4 ± 19.1	143.2 ± 18.6
Number of concomitant AEDs, n (%)				
1	13 (50.0)	9 (40.9)	11 (61.1)	33 (50.0)
2	8 (30.8)	12 (54.5)	6 (33.3)	26 (39.4)
3	5 (19.2)	1 (4.5)	1 (5.6)	7 (10.6)
Type of AEDs, n (%)				
Levetiracetam	8 (30.8)	7 (31.8)	3 (16.7)	18 (27.3)
Valproic Acid	10 (38.5)	8 (36.4)	9 (40.1)	27 (40.9)
Lamotrigine	6 (23.1)	6 (27.3)	4 (22.2)	16 (24.2)
Topiramate	1 (3.8)	0	1 (5.6)	2 (3.0)
Aged 17-65 years[b]	**n = 49**	**n = 50**	**n = 54**	**N = 153**
Age, years (mean ± SD)	31.3 ± 10.6	31.8 ± 9.7	31.6 ± 10.4	31.6 ± 10.2

(Continues)

TABLE 1 (Continued)

Aged 17-65 years[b]	n = 49	n = 50	n = 54	N = 153
Male (n, %)	21 (42.9)	19 (38.0)	23 (42.6)	63 (41.2)
Race, n (%)				
White	45 (91.8)	44 (88.0)	48 (88.9)	137 (89.5)
Asian	4 (8.2)	6 (12.0)	5 (9.3)	15 (9.8)
Other	0	0	1 (1.9)	1 (0.7)
Weight, kg (mean ± SD)	75.4 ± 18.5	72.1 ± 13.4	73.6 ± 12.9	73.7 ± 15.0
Height, cm (mean ± SD)	170.5 ± 11.2	169.2 ± 9.1	170.2 ± 9.3	170.0 ± 9.8
Number of concomitant AEDs, n (%)				
1	17 (34.7)	23 (46.0)	19 (35.2)	59 (38.6)
2	25 (51.0)	20 (40.0)	28 (51.9)	73 (47.7)
3	7 (14.3)	7 (14.0)	7 (13.0)	21 (13.7)
Type of AEDs, n (%)				
Levetiracetam	16 (32.7)	17 (34.0)	21 (38.9)	54 (35.3)
Valproic acid	8 (16.3)	9 (18.0)	12 (22.2)	29 (19.0)
Lamotrigine	9 (18.4)	12 (24.0)	12 (22.2)	33 (21.6)
Topiramate	12 (24.5)	10 (20.0)	9 (16.7)	31 (20.3)

Note: The safety set comprises all randomized patients who took at least one dose of the investigational product.

Abbreviations: AED, antiepileptic drug; GTC, primary generalized tonic-clonic; SD, standard deviation.

[a]No subjects had generalized clonic, tonic, atonic, or tonic/atonic seizures. Additionally, no subjects had a history of partial-onset seizures, status epilepticus, or unclassified epileptic seizure.

[b]Age at randomization.

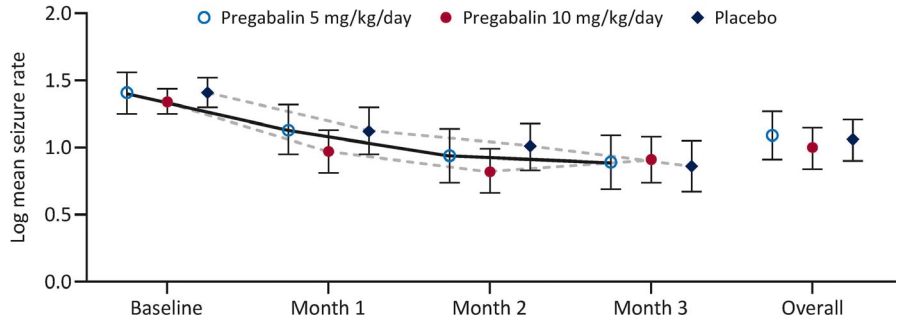

FIGURE 2 28-day GTC seizure rate during the double-blind, multicenter study (ITT population; primary endpoint). The primary endpoint was the log-transformed 28-day seizure rate for all GTC seizures collected during the double-blind assessment phase. The ITT population consisted of all randomized patients who took ≥1 dose of investigational product during the 12-week double-blind assessment phase, had a baseline value, and ≥1 postbaseline efficacy assessment (diary entry). GTC, generalized tonic-clonic and ITT, intent-to-treat

groups, respectively (Table S2). Median baseline 28-day seizure rate was 2.5 for all three groups. Median change from baseline was −1.01, −0.96, and −1.17, respectively. Change from baseline was similar in children and adults (Table S2).

3.4 | Responder rates (secondary efficacy analysis)

There were no notable differences between patients achieving ≥50% seizure reduction with either dose of pregabalin vs placebo in the overall analysis or by age-group (Figure 3).

3.5 | Exploratory endpoints

No significant differences in the mean proportion or number of seizure-free days (each type of seizure or for all seizures combined) were observed between either pregabalin treatment arm vs placebo (LS mean difference all seizure types vs placebo: 0.01 [P =.757] and −0.01 [P =.652], for 5 mg/kg/day and 10 mg/kg/day, respectively). Similarly, no significant differences in GTC seizure freedom (7% [P =.871] and 6% [P =.662], respectively) were observed between either pregabalin arm vs placebo and no significant change in number of seizure-free days gained (LS mean differences

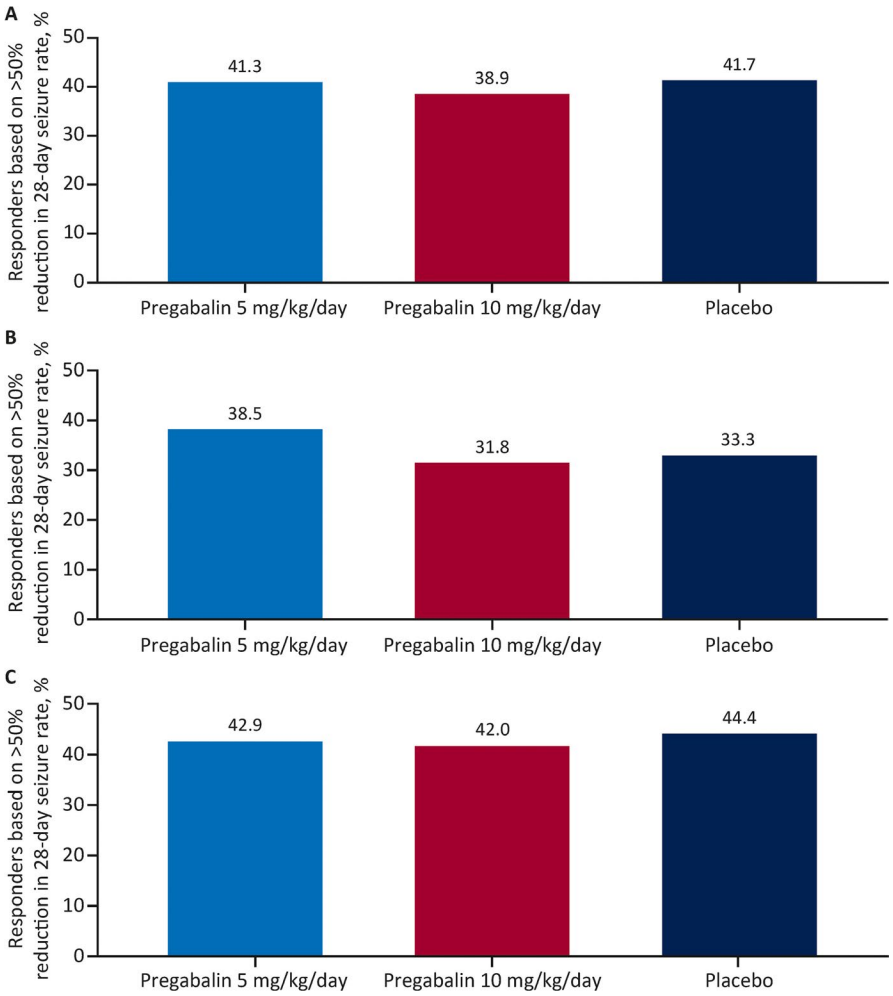

FIGURE 3 Patients with ≥50% reduction in 28-day GTC seizure rate (ITT population). A, Overall cohort. B, pediatric patients (aged 5-16 years), and C, adult patients (aged 17-65 years). GTC, primary generalized tonic-clonic and ITT, intent-to-treat

vs placebo 0.6 [P =.757] and −0.8 [P =.652] for all seizure types, respectively).

3.6 | Safety and tolerability

At least half of each treatment arm experienced ≥1 AE (53.5%, 56.9%, and 50.0% in the 5 mg/kg/day, 10 mg/kg/day, and placebo groups, respectively) (Table 2). The majority of AEs were mild or moderate in severity. The most frequently reported AEs (≥10% in any treatment group) were dizziness (17.3%) in 5 mg/kg/day group, dizziness (16.7%) and headache and somnolence (15.3%) in 10 mg/kg/day group, and headache (16.7%) with placebo (Table 2). No increase in the number of patients experiencing myoclonic seizures was observed in patients treated with pregabalin vs placebo: 29.3% and 27.8% patients in pregabalin 5 mg/kg/day and 10 mg/kg/day groups, respectively, experienced myoclonic seizures during the double-blind treatment phase vs 26.4% with placebo. In addition, 34.7% and 44.4%, respectively, experienced absence seizures vs 40.3% with placebo. One patient in the pregabalin 5 mg/kg/day group reported tonic-atonic seizures, and clonic seizures and unclassified epileptic seizures were reported by 1 patient each in the placebo group.

One death was reported of a 27-year-old Asian woman randomized to placebo. The cause of death was sudden unexpected death in epilepsy and was not considered to be related to study treatment. Other serious AEs were reported in six patients, and their resolution per treatment arm was (a) pregabalin 5 mg/kg/day: one adult (35 years) with GTC seizure, event led to discontinuation from the study (considered treatment-related), and one child (14 years) with status epilepticus, event led to discontinuation from the study (considered treatment-related); (b) pregabalin 10 mg/kg/day: one adult (35 years) with GTC seizure, event led to discontinuation from the study (considered treatment-related), and one child (6 years) with severe GTC seizure, which required hospitalization, study drug was discontinued on Day 22 due to insufficient clinical response, resolved on Day 25; and (c) placebo: two adults (25 and 26 years) with seizure events, both events led to discontinuation from the study, one serious AE was considered related to study drug.

No dose reductions or temporary discontinuations due to AEs were reported (Table 2). Seventeen patients (15 adults and 2 children) permanently discontinued treatment due to AEs. Two adults (both pregabalin 5 mg/kg/day) reported suicidal ideation

TABLE 2 All-causality AEs, overall and by age category (safety set)

	Pregabalin 5 mg/kg/day	Pregabalin 10 mg/kg/day, n (%)	Placebo, n (%)
Overall population	**n = 75**	**n = 72**	**n = 72**
Number of AEs	92	102	80
Patients: evaluable for AEs	75	72	72
With any AEs	40 (53.3)	41 (56.9)	36 (50.0)
With serious AEs	2 (2.7)	2 (2.8)	3 (4.2)
With severe AEs	3 (4.0)	3 (4.2)	2 (2.8)
Dose reduction or temporary discontinuation due to AEs	0	0	0
Permanent discontinuation due to AEs	8 (10.7)	5 (6.9)	4 (5.6)
Type of AE[a]			
Dizziness	13 (17.3)	12 (16.7)	5 (6.9)
Headache	7 (9.3)	11 (15.3)	12 (16.7)
Somnolence	5 (6.7)	11 (15.3)	7 (9.7)
Fatigue	5 (6.7)	3 (4.2)	3 (4.2)
UTI	4 (5.3)	2 (2.8)	4 (5.6)
Weight increased	1 (1.3)	7 (9.7)	0
Aged 5-16 years	**n = 26**	**n = 22**	**n = 18**
Number of AEs	22	19	15
Patients: evaluable for AEs	26	22	18
With any AE	13 (50.0)	11 (50.0)	8 (44.4)
With serious AEs	1 (3.8)	1 (4.5)	0
With severe AEs	1 (3.8)	1 (4.5)	0
Dose reduction or temporary discontinuation due to AEs	0	0	0
Permanent discontinuation due to AEs	2 (7.7)	0	0
Type of AE[a]			
Dizziness	4 (15.4)	1 (4.5)	0
UTI	3 (11.5)	2 (9.1)	3 (16.7)
Somnolence	2 (7.7)	2 (9.1)	1 (5.6)
Fatigue	2 (7.7)	0	1 (5.6)
Weight increased	1 (3.8)	2 (9.1)	0
Headache	1 (3.8)	2 (9.1)	1 (5.6)
Aged 17-65 years	**n = 49**	**n = 50**	**n = 54**
Number of AEs	70	83	65
Patients: evaluable for AEs	49	50	54
With any AE	27 (55.1)	30 (60.0)	28 (51.9)
With serious AEs	1 (2.0)	1 (2.0)	3 (5.6)
With severe AEs	2 (4.1)	2 (4.0)	2 (3.7)
Dose reduction or temporary discontinuation due to AEs	0	0	0
Permanent discontinuation due to AEs	6 (12.2)	5 (10.0)	4 (7.4)
Type of AE[a]			
Dizziness	9 (18.4)	11 (22.0)	5 (9.3)

(Continues)

TABLE 2 (Continued)

Aged 17-65 years	n = 49	n = 50	n = 54
Headache	6 (12.2)	9 (18.0)	11 (20.4)
Somnolence	3 (6.1)	9 (18.0)	6 (11.1)
Fatigue	3 (6.1)	3 (6.0)	2 (3.7)
Vertigo	3 (6.1)	2 (4.0)	1 (1.9)
Weight increased	0	5 (10.0)	0

Notes: The safety set comprises all randomized patients who took at least one dose of the investigational product.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI, urinary tract infection.

[a]In ≥2 patients taking pregabalin treatment arm (MedDRA (v21.1) preferred term).

or behaviors and required mental health risk assessments. One patient required mental health risk assessment twice during the study due to suicidal ideation; this patient was considered eligible to continue based on the results of the mental health risk assessments. A mental health risk assessment was performed for one further patient to evaluate a moderate AE of epileptic psychosis that previously resulted in discontinuation from the study, but the event had resolved by discontinuation.

4 | DISCUSSION

This randomized, placebo-controlled study of pregabalin treatment for the management of GTC seizures did not show any significant change in seizure frequency with adjunctive pregabalin treatment (10 mg/kg/day adjusted to 14 mg/kg/day in children with body weight <30 kg)[17,18] based on observed nonsignificant reduction in GTC seizure frequency compared with placebo treatment. This study was a postmarketing commitment investigating the safety of pregabalin in patients with GTC seizures, a type of epilepsy in which the benefit of adjunctive pregabalin had not been previously investigated in a randomized control trial. No increase in GTC seizure rate was seen, and the safety profile of pregabalin in this new population of patients was in line with previous observations of adjunctive pregabalin treatment for FOS, in both children and adults.[17,18,21,22,24] While some reports suggest an increase of myoclonic seizures in patients taking pregabalin,[28-30] this was not observed herein for either dose of pregabalin. It is important to note, however, that this study was not powered to detect differences in seizure type, other than GTC seizures.

The ideal goal of treatment with an AED is to eliminate seizures, but realistically the goal is to reduce seizure frequency to allow patients, of all ages, to maintain or return to a normal lifestyle while avoiding side effects from an AED regimen.[13] With different pharmacologic options for GTC seizures,[10,31] many patients can be treated successfully. However, some patients may not respond to any currently available pharmacologic treatments[16] or may require additional AEDs to control different types of seizure, which warrants investigations into alternative therapies with predictable safety profiles, such as pregabalin.

Pregabalin has a predictable and linear pharmacokinetic profile, making it an easy-to-use add-on AED with a predictable safety profile.[32] However, no study to date had investigated the efficacy and safety of pregabalin in adults and children with GTC seizures. The present study revealed no significant reduction in 28-day GTC seizure frequency with adjunctive pregabalin treatment compared with placebo treatment. Although no significant reduction in GTC seizure frequency or responder status was seen, pregabalin did not increase GTC or myoclonic seizures and demonstrated a safety profile consistent with the known safety profile in patients with other epileptic syndromes, including in adults and children with FOS.[17,18,26,33] The most common AEs reported in adults with FOS include dizziness, somnolence, and weight gain,[17] consistent with the common AEs recorded in this GTC population. We observed a gradual decline in GTC seizure frequency in all three treatment arms over the treatment period; however as patients were allowed to continue stable concomitant medications during the treatment phase, these may have influenced these observations. Studies have suggested an increasing placebo effect with ongoing AED treatments,[34] and some patients in the present study had suffered from GTC seizures for more than 50 years. The gradual decline in seizure frequency may also help explain the high responder rate observed in the placebo group.

There is a known peak in epilepsy incidence in young children, as well as older adults,[2-4] highlighting key populations at need for effective AED regimens. Although efficacy data can be extrapolated from adults to represent expected efficacy in children,[35] the safety profile of a drug is best studied in the population of interest. This study specifically recruited patients aged <16 years, per requirements from the FDA for this postmarketing safety commitment. As such, 66 children were recruited, of whom 48 were treated with pregabalin, thus adding to the safety information already available for pregabalin in children with epilepsy.[17-19] Importantly, no new safety signals were seen in these 48 children (4-16 years) with GTC seizures who received adjunctive pregabalin. AEs commonly observed in pediatric patients with FOS include somnolence and weight gain,[17-19] both of which were observed in ≥10% of patients in this GTC population, suggesting the safety profile of pregabalin is consistent regardless of seizure type. The discontinuation rate due to AEs was

relatively low (10.7%, 6.9%, and 5.6% with pregabalin 5 mg/kg/day, 10 mg/kg/day, and placebo, respectively), although we observed higher discontinuation rates due to AEs in adults (12.2%, 10.0%, and 7.4%, respectively) than in children (2%, 0%, and 0%, respectively). Discontinuations among adults were similar if somewhat lower than those seen in similar studies of pregabalin in adults patients with FOS.[23,24] These observations support a favorable safety profile of pregabalin, in line with that seen in other patient populations, including those with FOS.[16,18,21,23]

4.1 | Limitations

We conducted a multinational study, in 70 sites across 21 countries. This enabled a good representation of how pregabalin acts in a diverse population of adults and children with GTC seizures. The study protocol was specifically designed to limit the potential impact of variability in clinical practices, for example, a central reviewer model was used and concomitant medications for management of GTC seizures across different countries were limited. Despite these precautions, variability is inherent to multinational studies which enroll patients with different characteristics from different healthcare environments and cannot be eliminated altogether. In addition, seizures were captured by self-report in diaries, and therefore, data rely on the accuracy of these reports and the interpretation of seizure type by the person recording. In an attempt to improve accuracy of recording, diaries were routinely reviewed by study investigators together with patients or their guardians. However, any subjective rating of severity was not captured and therefore change in seizure severity could not be assessed based on diary data. These limitations are consistent with other international studies of seizures reliant on self-monitoring of events. Finally, despite being one of the most common seizure types, GCT seizures often occur less frequently than other types, for example, FOS. With a 2-week dose escalation phase followed by a 10-week fixed-dose phase and a 1-week taper phase, the study may not have been sufficient to detect changes in GCT seizure frequency in all patients. However, the overall number of patients enrolled ensured sufficient statistical power to detect changes in the overall study population during the designed length of study.

5 | CONCLUSIONS

In this postmarketing safety commitment study, adjunctive pregabalin did not change seizure rate in adults (17-65 years) or children (5-16 years) with GTC seizures. Pregabalin was well tolerated in adults and children with GTC seizures, and no increase in GTC seizure rate was noted. The safety profile observed was similar to that known for pregabalin treatment of adults and children with FOS.

ETHICAL PUBLICATION STATEMENT

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. The study protocols and amendments were reviewed and approved by the institutional review boards and independent ethics committees of the investigators' institutions and were in compliance with the ethical principles of the Declaration of Helsinki and with all International Council for Harmonisation good clinical practice guidelines. The study was rejected by the ethics committees in Italy and Portugal.

DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: (a) for indications that have been approved in the United States and/or EU; or (b) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

ACKNOWLEDGMENTS

Medical writing support was provided by Andrea Schauenburg, PhD, and Karen Burrows, PhD, of Engage Scientific Solutions, and was funded by Pfizer. The authors would like to acknowledge the 1105 study investigators. A full list of investigators is included in the supplementary materials (Table S1).

CONFLICT OF INTEREST

J Driscoll, M Almas, G Gregorian, J Liu, J Patrick, and J Antinew are full-time employees of Pfizer. JM Scavone was a full-time employee of Pfizer at the time of study conduct. A Kyrychenko has no conflict of interest to report. I Makedonska has no conflict of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Driscoll J, Almas M, Gregorian G, et al; the 1105 Study Group. Pregabalin as adjunctive therapy in adult and pediatric patients with generalized tonic-clonic seizures: A randomized, placebo-controlled trial. *Epilepsia Open*. 2021;6:381–393. https://doi.org/10.1002/epi4.12492