




ORIGINAL ARTICLE

Long-term open-label perampanel: Generalized tonic-clonic seizures in idiopathic generalized epilepsy

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Abstract

Objective: Assess the longer-term efficacy and safety of adjunctive perampanel (up to 12 mg/day) in patients aged ≥ 12 years with generalized tonic-clonic (GTC) seizures from the Open-label Extension (OLEx) Phase of Study 332 to determine whether responses obtained during the Core Study are maintained during long-term treatment.

Methods: Patients with GTC seizures previously enrolled in a randomized placebo-controlled trial of perampanel could enter an OLEx Phase comprising 6-week blinded conversion (during which patients previously randomized to placebo-switched to perampanel) and up to 136-week maintenance periods (maximum perampanel dose of 12 mg/day). A 4-week follow-up period was completed by all patients after the last on-treatment visit during the OLEx. We assessed seizure frequency outcomes from preperampanel baseline and the Core

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Study Pre-randomization Phase, retention rates, doses selected, and treatment-emergent adverse events (TEAEs).

Results: Overall, 138 patients entered the OLEx. Median percent reductions in GTC seizures per 28 days from preperampanel were 77% (Weeks 1-13) and 90% (Weeks 40-52). Retention rates were 88% (6 months) and 75% (12 months). Seizure-freedom rates were maintained for at least 2 years regardless of prior treatment received during the Core Study. Most common modal daily dose was >4-8 mg/day (n = 93). Across the Core and OLEx Phases, 120 (87%) patients experienced TEAEs; the most common was dizziness.

Significance: Perampanel was generally well-tolerated, and the TEAEs reported here are consistent with the known safety profile of perampanel. Perampanel offers a long-term treatment option for patients (aged ≥12 years) with GTC seizures.

KEYWORDS

epilepsy, generalized tonic-clonic seizures, Open-label Extension, perampanel

1 | INTRODUCTION

Limited treatment options are available for patients with treatment-resistant generalized tonic-clonic (GTC) seizures; thus, treatment with a narrow range of anti-seizure medications (ASMs) is often the only option for these patients.¹⁻³ Therefore, it is essential to continue to investigate ASMs with novel mechanisms of action to improve treatment outcomes for patients with GTC seizures.

Perampanel is a once-daily oral ASM approved for use in focal-onset seizures (previously partial-onset seizures), with or without progression to bilateral tonic-clonic seizures (previously secondarily generalized seizures), and GTC seizures (previously primary generalized tonic-clonic seizures).⁴ The approval of perampanel for the adjunctive treatment of GTC seizures was based on the randomized, double-blind, placebo-controlled, Phase 3 Study 332 in patients (aged ≥12 years) with idiopathic generalized epilepsy (IGE) and GTC seizures.¹ Patients who completed the Double-blind Phase of Study 332 could enter an Open-label Extension (OLEx) Phase.

Here, we investigated GTC seizure outcomes during longer-term treatment with perampanel (up to 12 mg/day) in patients who participated in the OLEx Phase of Study 332 to determine whether responses obtained during the Double-blind Phase are maintained during the OLEx. We report on the doses that were most likely to be selected for long-term use, and address longer-term tolerability and safety outcomes. We also evaluated retention rates, which is an outcome that addresses both efficacy and tolerability.

Key points

- The long-term safety/tolerability of adjunctive perampanel for GTC seizures was consistent with that observed in the double-blinded phase
- Seizure control was maintained for ≥2 years with adjunctive perampanel ≤12 mg/day in patients with uncontrolled GTC seizures in IGE
- The most common modal perampanel daily dose was >4-8 mg/day
- Long-term adjunctive perampanel may have a favorable risk-benefit ratio in patients aged ≥12 years with uncontrolled GTC seizures

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

Study 332 OLEx ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01393743) identifier: NCT01393743) was conducted at 69 sites in 16 countries across the US, Europe, and Asia-Pacific between July 2011 and October 2015. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC, and the US Code of Federal

Regulations Part 21. Trial protocol, amendments, and informed consent were reviewed by national regulatory authorities in each country and independent ethics committees or institutional review boards for each site. All patients gave written informed consent before participation.¹

2.2 | Study design

Patients (aged ≥12years) with GTC seizures in IGE who completed the prerandomization Phase (screening/

baseline) and the Double-blind, placebo-controlled, randomization Phase (4-week Titration; 13-week Maintenance) of Study 332 (i.e., Core Study), and who were otherwise eligible, had the option to enter the OLEx Phase (Figure 1A). The design of the Core Study and patient inclusion/exclusion criteria have been previously published.¹

The OLEx Phase comprised two parts: Part A (6-week blinded Conversion Period and 32-week Maintenance Period) and Part B (maximum of 104 week Maintenance). In addition, a 4-week Follow-up Period was to be completed by all patients after the last on-treatment visit in the

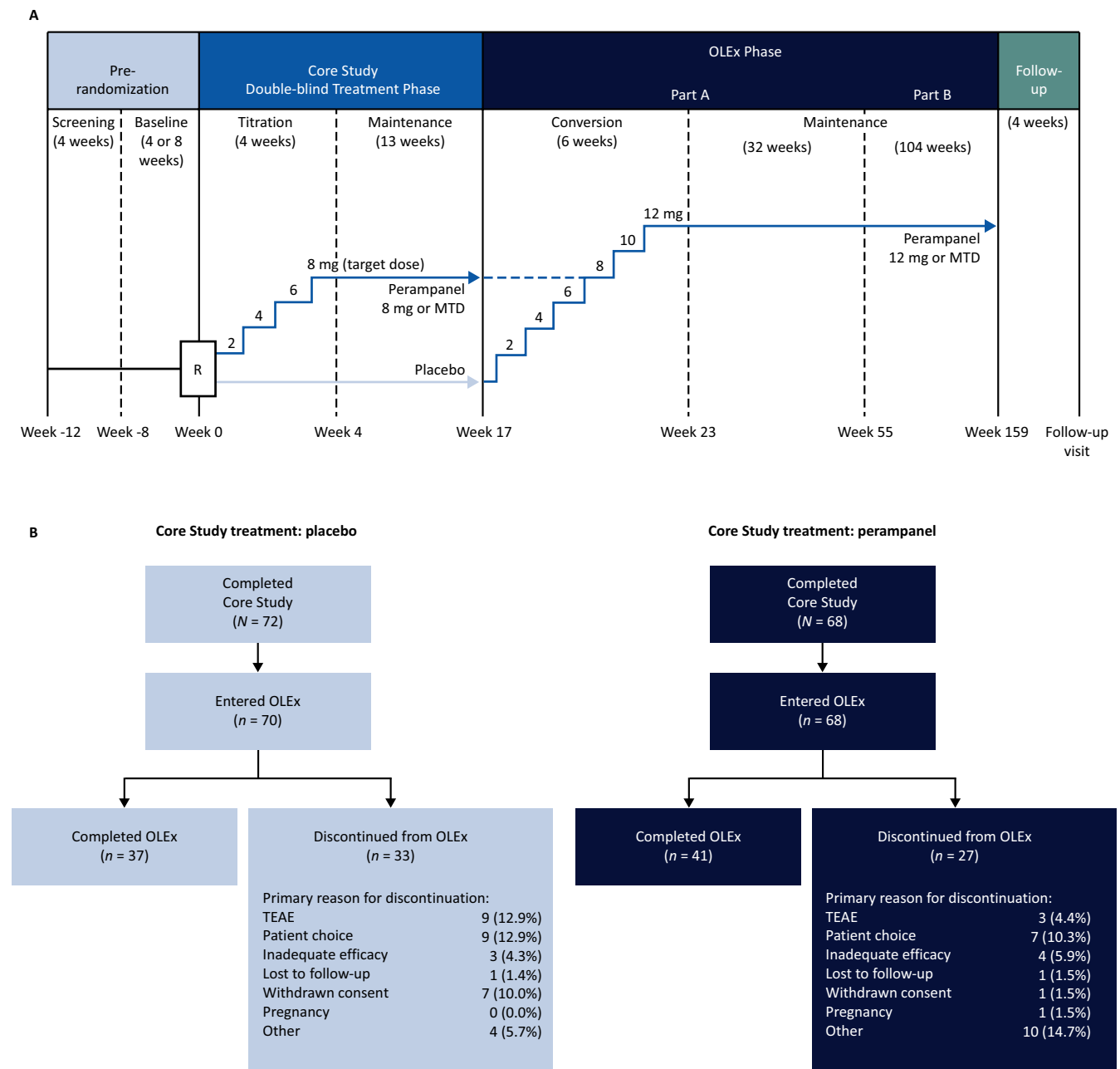


FIGURE 1 (A) Study design. Patients only needed to complete Part B (104 weeks) if perampanel was not commercially available. (B) Patient disposition by Core Study Treatment. Abbreviations: MTD, maximum tolerated dose; OLEx, Open-label Extension; R, randomization; TEAE, treatment-emergent adverse event

OLEx Phase. The OLEx Phase was terminated upon commercial availability of perampanel in the country where the patient resided.

During the Conversion Period, all patients and investigators remained blinded to treatment received in the preceding Core Study (perampanel 2-8 mg/day or placebo). Patients who had been assigned to placebo in the Core Study were started on blinded treatment with perampanel 2 mg/day and up-titrated weekly in 2-mg increments to the optimal dose per the investigator's discretion. Patients assigned to the perampanel arm in the Core Study continued to receive perampanel once daily on a blinded basis at the dose received during the Maintenance Period of the Core Study. Per the investigator's judgment, the dose of perampanel was decreased in the event of intolerance, and the dose of perampanel was increased up to 12 mg/day if needed for better seizure control until the optimal dose was found. Patients whose dose had been decreased could have their dose increased again once tolerability improved.

At the onset of the OLEx Maintenance Period, patients were unblinded to study treatment and remained on the optimal perampanel dose established during the blinded Conversion Period. Dose adjustment during the Maintenance Period was allowed if medically necessary per the investigator's discretion. All perampanel dose adjustments (upwards or downwards) were done in 2-mg increments and patients who did not tolerate a minimum dose of 2 mg/day during the OLEx Phase were discontinued from the study. The maximum dose of perampanel allowed during the OLEx Phase was 12 mg/day.

Patients entered the OLEx Phase on the same concomitant ASMs as they were receiving at the end of the Core Study. During the OLEx Maintenance Period, changes to concomitant ASMs (addition, deletion, or dose adjustment) were allowed, with care taken when switching between an inducer and noninducer ASM.

Duration of participation in Part B of the OLEx Phase was dependent upon the patient's total number of weeks of exposure to perampanel, and the timing of Part A completion relative to the Core Study data review. Patients who elected to participate in Part B were treated until they had at least 52 weeks of total exposure to perampanel. If a positive risk-benefit assessment for the treatment of GTC seizures was demonstrated, patients in a country where an extended access program (EAP) had been activated ended treatment under this protocol and were given the option to enroll in the EAP. If an EAP had not been activated in their country, patients ended treatment under this protocol and continued to the Follow-up Period of the OLEx Phase. Patients who elected not to participate in Part B ended treatment and continued to the Follow-up Period of the OLEx Phase.

2.3 | Efficacy assessments

Efficacy analyses were based on the Full Analysis Set (FAS), which comprised all patients who were eligible to participate in the OLEx Phase, received ≥ 1 dose of perampanel in the OLEx, and had baseline seizure frequency data and ≥ 1 observation of valid seizure diary data during the perampanel treatment duration. Seizure diary data were recorded daily until the end of study Part A up to 55 weeks (diary collection was stopped at the start of study Part B). Any days with missing diary entries were classed as seizure-free days. Efficacy assessments included median percent change in seizure frequency per 28 days, 50% responder rates (defined as the proportion of patients with a $\geq 50\%$ reduction in seizure frequency per 28 days), and seizure-freedom rates, all relative to preperampanel baseline and the Core Study Pre-randomization Phase. In addition, analyses were performed for patients who achieved freedom from GTC or all seizures for a period of at least 6 or 12 months, stratified by treatment received in the Core Study (prior placebo or prior perampanel).

Due to the potential bias resulting from those patients who had a better response tending to remain in the study for a longer duration, a post hoc analysis was performed in which populations who had remained in the study for specific durations were assessed to see if, for these populations, efficacy was maintained over time. For this analysis, the OLEx population was subdivided into those that remained in the study for at least 26 weeks ($n = 125$), 39 weeks ($n = 120$), 1 year ($n = 109$), or 2 years ($n = 44$).

2.4 | Safety assessments

Safety assessments were based on the Safety Analysis Set (SAS), which included patients who received ≥ 1 dose of perampanel in the OLEx Phase and had any on-treatment safety data during this phase. Retention rates on perampanel at 6 months, 1 year, and 2 years were assessed in the SAS, where retention rate was defined as the number of patients on treatment for at least x months/the number of patients who could have been on treatment for at least x months. Treatment-emergent adverse events (TEAEs), serious TEAEs, and treatment discontinuation were all monitored throughout the study. TEAEs of special interest were also assessed using Medical Dictionary for Regulatory Activities Version 16.1. (MedDRA) Standardized MedDRA Queries (SMQs). TEAEs included adverse events (AEs) that occurred from the first day of perampanel administration (in the Core Study or OLEx Phase) to 30 days after the last dose of perampanel, or that were present before the first day of perampanel administration but worsened in severity during the study. TEAEs

were considered serious if they were life-threatening (e.g., suicide attempt), or involved hospitalization or prolonged hospitalization. Suicidality (suicidal ideation and behavior) was measured using the Columbia Suicide Severity Rating Scale (C-SSRS) at each study visit. C-SSRS responses were reviewed by the investigator to determine whether any positive results constituted a TEAE of suicidality; only the events that were deemed a TEAE of suicidality are reported and discussed here.

Prior and concomitant medication usage, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, and changes in physical and neurological examinations were also assessed. In addition, a withdrawal questionnaire was administered to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel.

2.5 | Statistical analyses

All data are presented descriptively, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints.

2.6 | Data accessibility statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3 | RESULTS

3.1 | Patients

In total, 140 patients completed the Core Study and were eligible to enter the OLEx Phase. Of these, 138 patients entered the OLEx Phase (70 placebo, 68 perampanel), representing 98.6% of the patients who completed the Core Study (Figure 1B). All 138 patients in the OLEx Phase received ≥ 1 dose of perampanel and were included in the SAS. Table 1 shows baseline demographics and clinical characteristics for patients in the FAS/SAS. There was an observed female predominance in the study population (57.2% female vs 42.8% male) similar to previous IGE studies.^{5,6}

Overall, 34.8% of patients in the SAS were taking one concomitant ASM, 44.2% were taking two, and 20.3% were taking three at the Core Study baseline. The most common ASMs were lamotrigine (41.3%), valproic acid (32.6%), levetiracetam (29.0%), topiramate (16.7%), zonisamide (10.9%), and extended-release valproate (10.1%); all

other background ASMs were taken by less than 10% of patients (Table 1). Of note, 13 (9.4%) patients were taking carbamazepine, 7 (5.1%) were taking phenytoin, and 5 (3.6%) were taking oxcarbazepine during the OLEx Phase.

Across all patients who received perampanel, 78/138 (56.5%) patients completed the OLEx Phase. The most common primary reasons for discontinuation of perampanel during the OLEx Phase were patient choice (11.6%), other (10.1%), and AEs (8.7%) (Figure 1B).

3.2 | Efficacy outcomes

3.2.1 | Efficacy relative to preperampanel baseline

Across the entire perampanel treatment duration (Core Study and OLEx Phase), median percent reductions in seizure frequency per 28 days achieved during the first 3-6 months of adjunctive perampanel treatment relative to preperampanel baseline were maintained for at least 2 years for GTC seizures (Figure 2Ai) and all seizures (Figure 2Aii). In each patient cohort, over half of patients experienced a $\geq 50\%$ reduction in seizure frequency for GTC seizures (Figure 2Bi) and all seizures (Figure 2Bii) during each 13-week treatment interval, regardless of perampanel exposure time. Similarly, seizure-freedom rates achieved following 3-6 months of adjunctive perampanel treatment were maintained for at least 2 years in patients with GTC seizures (Figure 2Ci) and all seizures (Figure 2Cii).

3.2.2 | Efficacy relative to Core Study Pre-randomization Phase

In patients who received perampanel during the Core Study, median percent reductions in seizure frequency per 28 days achieved during the Core Study Maintenance Phase relative to the Core Study Pre-randomization Phase were maintained during long-term treatment in the OLEx for GTC seizures (Figure 3Ai) and all seizures (Figure 3Aii). In patients who received placebo during the Core Study, median percent reductions in seizure frequency per 28 days were greater during the OLEx Phase as compared with the Core Study (Figures 3Ai,Aii). Fifty-percent responder rates were also maintained from the Core Study to the OLEx Phase, with over half of patients receiving placebo or perampanel in the Core Study achieving a $\geq 50\%$ reduction in GTC seizure frequency at each treatment interval (Figure 3Bi) and at least 40% of patients achieving a $\geq 50\%$ reduction in the frequency of all seizures at each treatment interval

TABLE 1 Patient demographics and clinical characteristics at baseline by Core Study treatment

	Core Study treatment		Total (N = 138)
	Placebo (n = 70)	Perampanel (n = 68)	
Mean (SD) age, ^a years	29.1 (12.1)	26.6 (9.9)	27.9 (11.1)
Age group, ^a n (%)			
<18 years	8 (11.4)	11 (16.2)	19 (13.8)
≥18 to <65 years	61 (87.1)	57 (83.8)	118 (85.5)
≥65 years	1 (1.4)	0 (0.0)	1 (0.7)
Sex, n (%)			
Male	30 (42.9)	29 (42.6)	59 (42.8)
Female	40 (57.1)	39 (57.4)	79 (57.2)
Race, n (%)			
Caucasian	37 (52.9)	34 (50.0)	71 (51.4)
Asian	30 (42.9)	31 (45.6)	61 (44.2)
Black or African American	2 (2.9)	1 (1.5)	3 (2.2)
Other	1 (1.4)	2 (2.9)	3 (2.2)
Mean (SD) time since diagnosis, ^b years	18.8 (12.8)	14.8 (10.2)	16.8 (11.7)
History of seizure type, ^b n (%)			
Tonic-clonic	70 (100.0)	68 (100.0)	138 (100.0)
Myoclonic	31 (44.3)	28 (41.2)	59 (42.8)
Absence	35 (50.0)	34 (50.0)	69 (50.0)
Clonic	1 (1.4)	0 (0.0)	1 (0.7)
Tonic	2 (2.9)	0 (0.0)	2 (1.4)
No. of concomitant ASMs at baseline, ^c n (%)			
One	25 (35.7)	23 (33.8)	48 (34.8)
Two	30 (42.9)	31 (45.6)	61 (44.2)
Three	14 (20.0)	14 (20.6)	28 (20.3)
Most common (≥10% of total patients) concomitant ASMs, ^{c,d} n (%)			
Lamotrigine	28 (40.0)	29 (42.6)	57 (41.3)
Valproic acid	23 (32.9)	22 (32.4)	45 (32.6)
Levetiracetam	15 (21.4)	25 (36.8)	40 (29.0)
Topiramate	6 (8.6)	17 (25.0)	23 (16.7)
Zonisamide	11 (15.7)	4 (5.9)	15 (10.9)
Extended-release valproate	7 (10.0)	7 (10.3)	14 (10.1)

Abbreviations: ASM, anti-seizure medication; No., number; SD, standard deviation.

^aAge is calculated on the date of informed consent in the Core Study.

^bTime since diagnosis and history of seizure type(s) are with respect to date of informed consent in the core study. If the day or month of diagnosis was missing, the day was imputed to be the first of the month, and the month was imputed to be January. If the imputed date was before the birth date, the birth date was used in place of the date of diagnosis.

^cBased on the safety analysis set; all other data are based on the full analysis set.

^dPatients reporting the same ASM more than once are counted only once.

(Figure 3Bii). In addition, seizure-freedom rates were also maintained from the Core Study to the OLEx Phase (Figures 3Ci,Cii). Overall, 57.4% and 33.8% of patients who received perampanel during the Core Study and OLEx Phase achieved seizure freedom from GTC seizures for a period of at least 6 or 12 months, respectively (Figure 3Di). In patients who received placebo during the Core Study before converting to perampanel during the OLEx Phase, 48.6% and 25.7% of patients were GTC seizure-free for at least 6 and 12 months, respectively (Figure 3Di). For all seizure types, 39.7% and 22.1% of patients who received perampanel during the Core Study and 35.7% and 17.1% of patients who received placebo during the Core Study were free from all seizures for at least 6 or 12 months, respectively (Figure 3Dii).

Among patients who received prior treatment with placebo during the Core Study, the median percent reduction in GTC seizure frequency and both the 50% responder and seizure-freedom rates increased to a level similar to that for patients who received treatment with perampanel during the Core Study by the end of the OLEx blinded Conversion Period.

3.3 | Safety outcomes

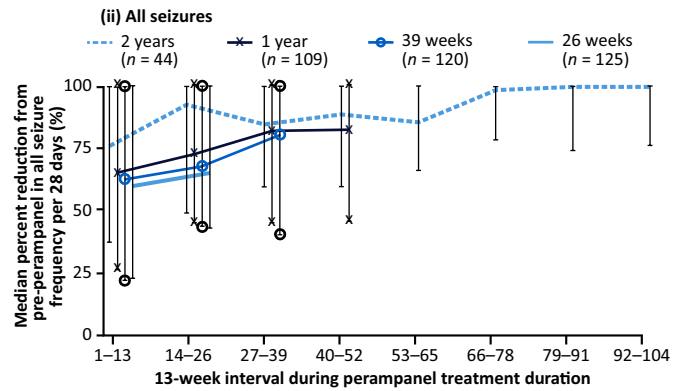
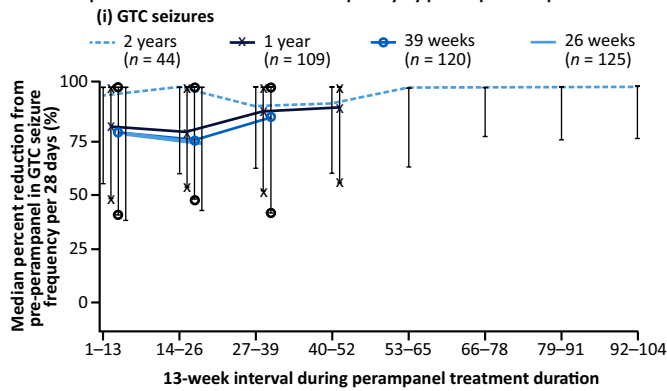
3.3.1 | Perampanel exposure

The cumulative extent of exposure to perampanel across the Core Study and OLEx Phase is summarized by modal daily dose for the SAS in Figure S1. The mean (standard deviation [SD]) duration of perampanel exposure was 83.9 (38.4) weeks (range: 2.4-161.7 weeks), and 79.0% of patients in the SAS received more than 52 weeks of perampanel treatment. The total exposure to perampanel was 11 578.9 patient-weeks.

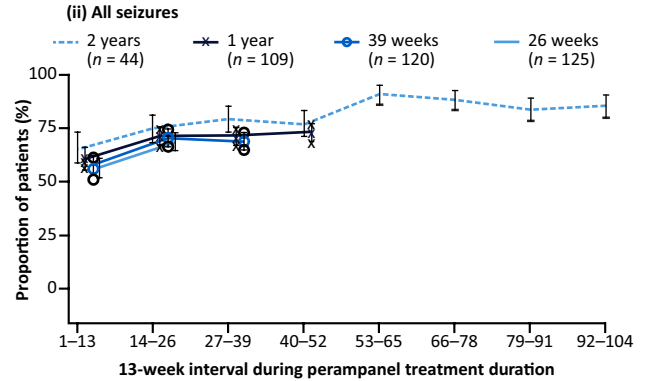
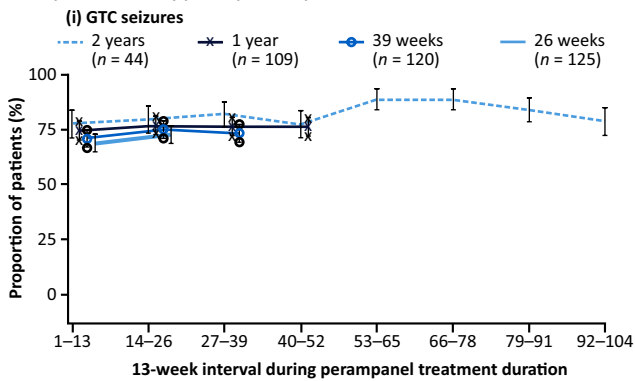
3.3.2 | Perampanel dose

Of 138 patients treated with perampanel during the OLEx Phase, two patients received a modal daily dose of <4 mg/day, nine received a modal daily dose of 4 mg/day, 93 received a modal daily dose of >4-8 mg/day, and 34 received a modal daily dose of >8-12 mg/day. The mean (SD) dose of perampanel across the OLEx Phase was 8.0 (2.0) mg/day (range: 2-12 mg/day) for the SAS. The mean (SD) dose during the OLEx Conversion Period was 6.8 (1.4) mg/day (range: 3-11 mg/day) and for the OLEx Maintenance Period was 8.2 (2.1) mg/day (range: 2-12 mg/day). It should be noted that the mean dose during conversion was lower

A Median percent reduction in seizure frequency by perampanel exposure



B 50% responder rates by perampanel exposure



C Seizure-freedom rates by perampanel exposure

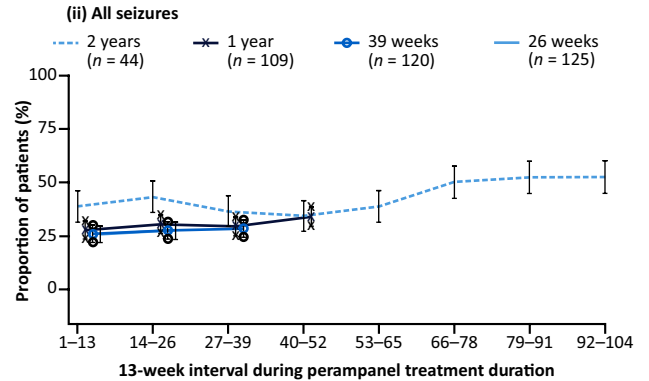
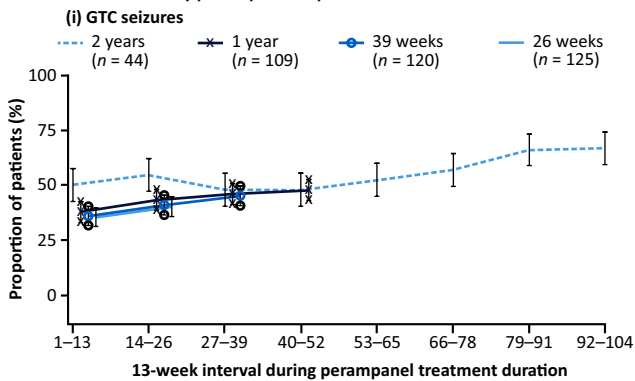


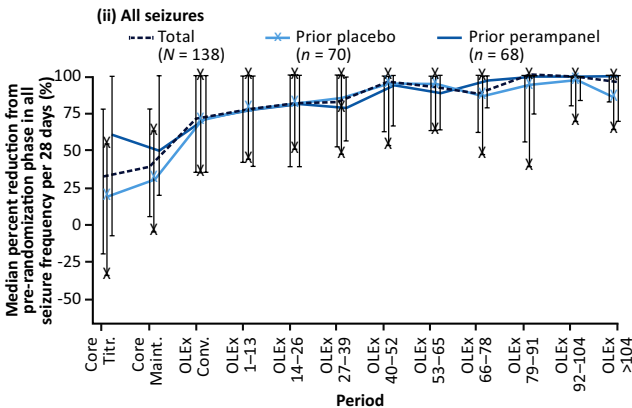
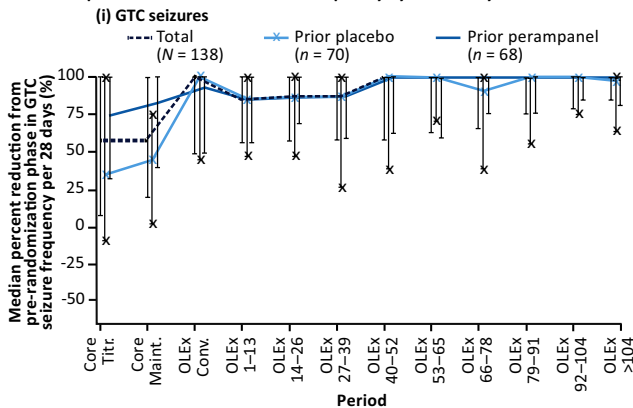
FIGURE 2 Efficacy from preperampanel baseline for (i) GTC seizures and (ii) all seizures. Abbreviations: GTC, generalized tonic-clonic; OLEx, Open-label Extension. Full analysis set. Data are presented by 13-week treatment intervals. Week 1 begins on the date of first dose of the perampanel treatment duration. The perampanel treatment duration starts on the date of the first dose of perampanel, regardless of whether this occurred in the Core Study or OLEx Phase and continues to, and includes, the date of the last dose of perampanel in the OLEx Phase. Error bars represent standard errors

than during maintenance since half of patients were up-titrating during that time. For patients who completed the OLEx Phase (N = 78), last daily perampanel doses were: 2 mg/day (n = 3 [3.8%]), 4 mg/day (n = 7 [9.0%]), 6 mg/day (n = 8 [10.3%]), 8 mg/day (n = 41 [52.6%]), 10 mg/day (n = 6 [7.7%]), and 12 mg/day (n = 13 [16.7%]).

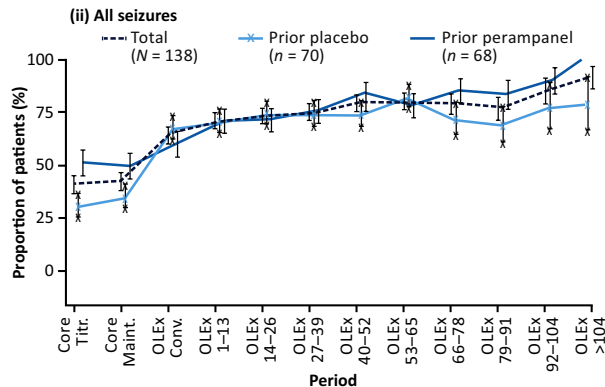
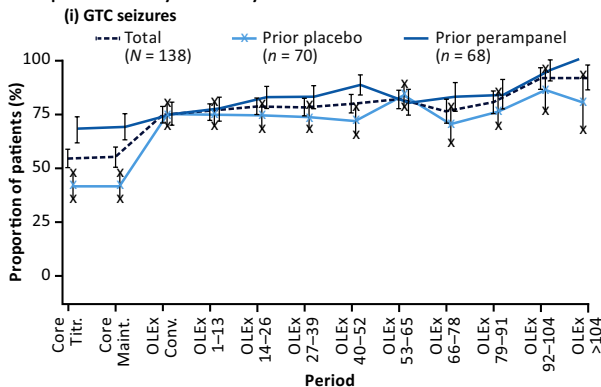
During the OLEx Phase, 33 patients increased their daily perampanel dose and 23 patients decreased their daily dose (there may have been some overlap between

these groups). Dose increases occurred in 1/4 (25.0%), 7/18 (38.9%), 15/86 (17.4%), and 10/15 (66.7%) patients who were receiving a daily dose of 4, 6, 8, and 10 mg/day at the start of the OLEx Maintenance Period, respectively. Dose decreases occurred during the OLEx in 0/4 (0.0%), 1/18 (5.6%), 15/86 (17.4%), 3/15 (20.0%), and 4/10 (40.0%) patients who were receiving a daily dose of 4, 6, 8, 10, and 12 mg/day at the start of the OLEx Maintenance Period, respectively.

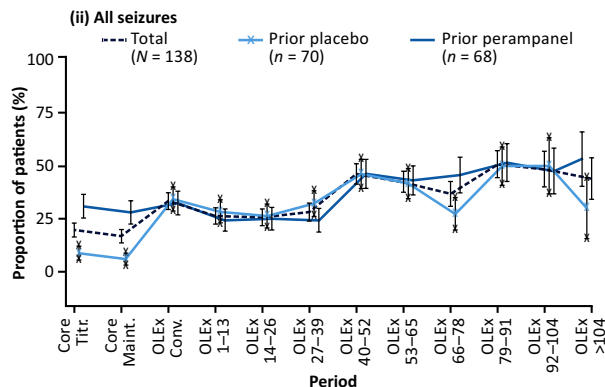
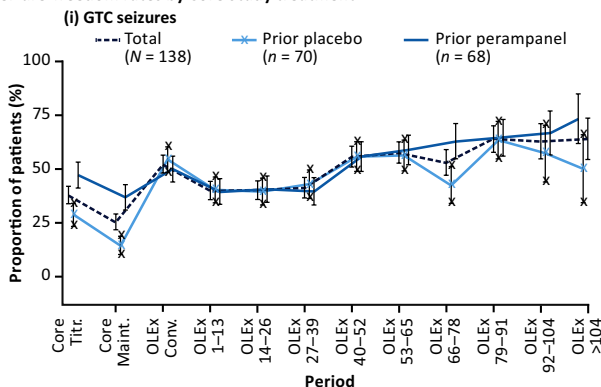
A Median percent reduction in seizure frequency by Core Study treatment



B 50% responder rates by Core Study treatment



C Seizure-freedom rates by Core Study treatment



D Seizure-freedom rates for 6 and 12 months by Core Study treatment

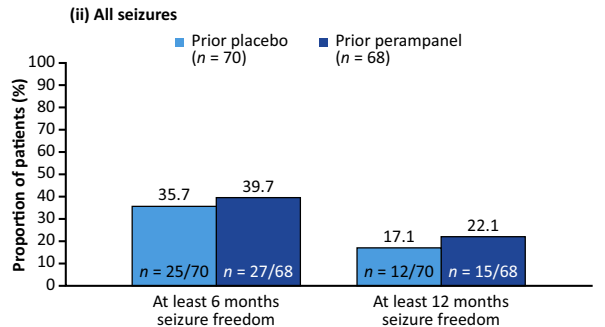
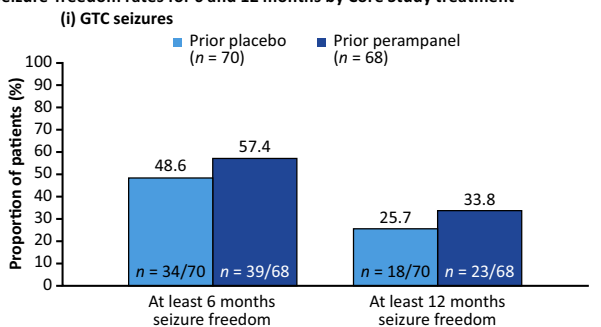


FIGURE 3 Efficacy from Core Study Pre-randomization Phase for (i) GTC seizures and (ii) all seizures. Abbreviations: Conv., conversion; GTC, generalized tonic-clonic; Main., Maintenance; OLEx, Open-label Extension; Titr., Titration. Full analysis set. Data are presented by treatment period. Week 1 begins on the date of first dose of the perampanel treatment duration. The perampanel treatment duration starts on the date of the first dose of perampanel, regardless of whether this occurred in the Core Study or OLEx Phase and continues to, and includes, the date of the last dose of perampanel in the OLEx Phase. Error bars represent standard errors

3.3.3 | Retention rates

The retention rate at 6 months was 88.4% ($n = 122/138$), at 1 year was 74.6% ($n = 103/138$) and at 2 years was 49.2% ($n = 31/63$). Note that study closure and other administrative reasons affected the number of patients included in the calculation of retention rate at 2 years. At 6 months and 1 year, retention rates were slightly higher in the prior perampanel group (92.6% [$n = 63/68$] and 76.5% [$n = 52/68$], respectively) compared with the prior placebo group (84.3% [$n = 59/70$] and 72.9% [$n = 51/70$], respectively), and at 2 years were slightly higher in the prior placebo group (61.9% [$n = 13/21$]) vs the prior perampanel group (42.9% [$n = 18/42$]). However, at each time point, the actual number of patients retained on treatment was similar in both groups.

3.3.4 | Treatment-emergent adverse events

Overall, 120 (87.0%) patients experienced TEAEs across the Core Study and OLEx Phase (Table 2). The most common TEAE in each perampanel modal dose group was dizziness (35.3%-100.0% across groups; Table 2).

Serious TEAEs were reported in 18 (13.0%) patients, with the highest incidence occurring in patients receiving a modal dose of >8-12 mg/day ($n = 8/34$ [23.5%]). The most common serious TEAEs were convulsion ($n = 3$ [2.2%]) and suicide attempt ($n = 2$ [1.4%]). All but two of the nonfatal serious TEAEs had been resolved by the end of the study. In addition to two deaths that occurred during the Core Study, there was one death during perampanel exposure in the OLEx Phase that occurred in a patient who received 6 mg/day during the Core Study and 10 mg/day during the OLEx Phase. This death occurred 64 days after the last dose on study day 380 (day 261 of the OLEx). The cause of death was due to treatment-emergent acute pancreatitis and was assessed by the investigator as not related to study treatment.

Treatment-emergent adverse events resulting in discontinuation of perampanel treatment occurred in 13 (9.4%) patients. The two events that resulted in the discontinuation of ≥ 2 patients were dizziness and suicide attempt (Table 2). Two of the three patients who discontinued due to TEAEs of dizziness were receiving 8 mg/day, and the third patient was receiving 12 mg/day. The two patients who discontinued due to TEAEs of suicide attempt were receiving 8 and 12 mg/day at the time of the suicide attempt.

Regarding TEAEs of special interest, eight patients (5.8%) who experienced TEAEs of suicidality as determined by the investigator: five patients experienced suicidal ideation, two patients attempted suicide, and one

patient engaged in self-injurious behavior. One of the five patients who experienced a TEAE of suicidal ideation had a history of anxiety, bipolar disorder, and depression prior to the study. As noted above, the two suicide attempts were serious and resulted in treatment discontinuation; all events were resolved. One patient who attempted suicide had reported a serious TEAE of depression prior to the suicidality event and received citalopram for the treatment of depression.

Treatment-emergent adverse events related to alertness and cognition were reported in 35 (25.4%) patients; the most common of these events ($\geq 2\%$) were somnolence ($n = 18$ [13.0%]), aggression ($n = 4$ [2.9%]), agitation ($n = 3$ [2.2%]), initial insomnia ($n = 3$ [2.2%]), mood swings ($n = 3$ [2.2%]), and altered mood ($n = 3$ [2.2%]).

Treatment-emergent adverse events related to hostility/aggression were reported in 8 (5.8%) patients using narrow SMQ terms, and 30 (21.7%) patients using narrow and broad SMQ terms. The most common TEAEs related to hostility/aggression using the narrow SMQ criteria were aggression ($n = 4$ [2.9%]) and anger ($n = 3$ [2.2%]); the most common using the narrow and broad SMQ criteria was irritability ($n = 19$ [13.8%]). One event of aggression was a serious TEAE. TEAEs related to psychosis and psychotic disorders were reported in 3 (2.2%) patients using narrow SMQ terms and 8 (5.8%) patients using narrow and broad SMQ terms. The most common of these using the narrow SMQ criteria was visual hallucination ($n = 2$ [1.4%]), and using the narrow and broad SMQ criteria was abnormal behavior ($n = 2$ [1.4%]). There were no events that were considered serious and none that led to discontinuation.

Treatment-emergent adverse events related to status epilepticus or convulsions occurred in 10 (7.2%) patients. Four of these TEAEs were serious (three patients receiving 8 mg/day and one receiving 10 mg/day). None of these TEAEs resulted in treatment discontinuation. TEAEs related to drug-related hepatic disorder abnormalities were reported in four (2.9%) patients: two patients experienced events of increased aspartate aminotransferase (one patient receiving 12 mg/day and one receiving 2 mg/day); one patient experienced hepatopathy (2 mg/day); and one patient experienced hyperammonemia (10 mg/day). None of these events were serious or resulted in treatment discontinuation, and all patients recovered.

3.3.5 | Laboratory results and vital signs

There were no clinically important mean changes in hematology or clinical chemistry laboratory values during exposure to perampanel in the Core Study and/or OLEx Phase. Mean changes from baseline to the end of treatment in blood pressure and heart rate across all perampanel

TABLE 2 Overview of TEAEs and most common TEAEs by modal daily perampanel dose

	Modal daily perampanel dose (mg/day)				Total (N = 138)
	<4 (n = 2)	4 (n = 9)	>4-8 (n = 93)	>8-12 (n = 34)	
TEAEs, ^a n (%)	2 (100.0)	8 (88.9)	82 (88.2)	28 (82.4)	120 (87.0)
Treatment-related TEAEs, ^b n (%)	2 (100.0)	8 (88.9)	67 (72.0)	22 (64.7)	99 (71.7)
Severe TEAEs, n (%)	0 (0.0)	2 (22.2)	9 (9.7)	9 (26.5)	20 (14.5)
Serious TEAEs, n (%)	0 (0.0)	1 (11.1)	9 (9.7)	8 (23.5)	18 (13.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.7)
Most common (≥10% of total patients) TEAEs, ^c n (%)					
Dizziness	2 (100.0)	5 (55.6)	34 (36.6)	12 (35.3)	53 (38.4)
Nasopharyngitis	0 (0.0)	1 (11.1)	13 (14.0)	6 (17.6)	20 (14.5)
Irritability	0 (0.0)	2 (22.2)	13 (14.0)	4 (11.8)	19 (13.8)
Upper respiratory tract infection	0 (0.0)	3 (33.3)	9 (9.7)	6 (17.6)	18 (13.0)
Somnolence	0 (0.0)	2 (22.2)	14 (15.1)	2 (5.9)	18 (13.0)
Headache	0 (0.0)	2 (22.2)	12 (12.9)	3 (8.8)	17 (12.3)
Vertigo	0 (0.0)	1 (11.1)	13 (14.0)	1 (2.9)	15 (10.9)
Fatigue	0 (0.0)	2 (22.2)	9 (9.7)	3 (8.8)	14 (10.1)
Most common (≥2 patients) TEAEs leading to discontinuation, ^c n (%)					
Dizziness	0 (0.0)	1 (11.1)	2 (2.2)	0 (0.0)	3 (2.2)
Suicide attempt	0 (0.0)	0 (0.0)	1 (1.1)	1 (2.9)	2 (1.4)

Note: Safety analysis set. AEs were summarized across the entire perampanel exposure. For patients who received placebo during the Core Study, perampanel exposure consists of the OLEx Phase; for patients who received perampanel during the Core Study, perampanel exposure consists of both the Core Study and OLEx Phase. A patient with ≥2 AEs with the same preferred term is counted only once for that preferred term.

Abbreviations: AE, adverse event; OLEx, Open-label Extension; TEAE, treatment-emergent adverse event.

^aAn AE was considered treatment-emergent if the AE started on, or after, the date of the first perampanel dose and prior to, or on, the day of (date of last dose +30 days) during the OLEx Phase.

^bIncludes TEAEs considered by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.

^cMedical Dictionary for Regulatory Activities Version 16.1.

doses were less than or equal to ± 3.8 mmHg or 6.4 beats per minute, respectively. Across the entire perampanel treatment duration, 39.1% of patients had a clinically notable increase in body weight and 13.0% had a clinically notable decrease in body weight. At the end of treatment, the mean change from baseline in body weight across all doses was 2.5 kg (range: -9-20.6).

4 | DISCUSSION

Tonic-clonic seizures are among the most serious and harmful seizures and are associated with injury and sudden unexpected death in epilepsy.^{1,2,7-11} They are also one of the only seizure types in which occurrence has been associated with cognitive decline.^{2,12} Perampanel was previously shown to be efficacious and well-tolerated in the randomized, Double-blind Phase of Study 332.¹ However, the aim of the OLEx study was to assess whether seizure reductions are enduring, particularly seizure freedom

since these data are important to determine the long-term efficacy of an ASM.

When assessing long-term outcomes in open-label studies, it is important to account for study drop-outs, as populations who stay longer tend to be enriched for patients with a better response. We addressed this by looking at patients with 26 weeks, 39 weeks, 1 year, or 2 years of perampanel exposure and assessing whether seizure frequency increased, decreased, or remained the same over time. Our results show that patients in each cohort experienced reductions in seizure frequencies for both GTC seizures and all seizures compared with pretreatment and that this effect was maintained over time.

We also determined that efficacy established in the Core Study for the perampanel arm was maintained during the OLEx Phase, while efficacy was improved for the placebo arm when these patients were transitioned to perampanel during the OLEx Phase. Furthermore, by the end of the blinded Conversion Period of the OLEx Phase, patients who had received prior treatment with placebo

during the Core Study had similar efficacy as patients who received perampanel, suggesting that a delay in the initiation of adjunctive perampanel treatment does not negatively affect long-term seizure control.

The high seizure requirement for this study necessitated by the study design (three observable seizures during 8 weeks of baseline) could impact the generalizability of patients with less frequent seizures. A multicenter, retrospective, observational study showed that perampanel was associated with improved seizure outcomes, irrespective of seizure type, in the clinical care of patients with IGE, and 4 mg was the most common dose.¹³ However, interpretations of the use of perampanel ≤ 4 mg/day in Study 332 may be limited due to the small number of patients ($n = 11$). Given the use of perampanel ≤ 4 mg/day may be of interest to patients with less severe IGE, further evaluation of perampanel in the clinic will be helpful in this regard.

Taken together, our data show that perampanel is efficacious for the long-term treatment of GTC seizures in patients with IGE. Since some ASMs have previously been shown to aggravate certain seizure types in IGE, such as myoclonic and absence seizures,^{14–16} it is also important to assess the effects of ASMs on these other seizure types. A recent post hoc analysis based on Study 332 showed that the median percent reduction in the frequency of myoclonic seizures per 28 days from the Core Study Pre-randomization Phase was 52.5% (placebo) vs 24.5% (perampanel); for absence seizures, this was 7.6% (placebo) vs 41.2% (perampanel).¹⁷ Seizure-freedom rates of myoclonic seizures were 13.0% (placebo) vs 16.7% (perampanel); for absence seizures, these were 12.1% (placebo) vs 22.2% (perampanel). Responses during the Core Study were maintained during long-term (>104 weeks) adjunctive perampanel treatment, suggesting that perampanel does not worsen myoclonic or absence seizures in patients with GTC seizures in IGE.¹⁷

During the OLEx Phase of Study 332, no new AE signals were uncovered compared with the Core Study and the known safety profile of perampanel.¹⁴ Furthermore, serious AE profiles were similar to those observed during long-term treatment in the focal epilepsy population.¹⁸ With regard to the eight patients who experienced TEAEs of suicidality (as determined by the investigator), one patient had a medical history of depression prior to the study, and one patient experienced a serious TEAE of depression prior to the event of suicidal attempt. Even though the incidence of suicidality following perampanel treatment is low, patients receiving perampanel should be monitored for signs of psychiatric TEAEs as recommended in the class label of ASMs; and perampanel dose adjustments may be considered to manage symptoms of psychiatric TEAEs.

A limitation of this study was the open-label design, meaning that no control arm was included. In addition, the study presented some confounders, including changes in background ASMs from baseline to the end of treatment (summarized in Table S1) and the potential association between treatment duration and tolerability, which could have influenced the results. Another limitation of this study was that participants were predominantly Caucasian or Asian, which may limit the generalizability of the findings to other groups.

5 | CONCLUSIONS

Seizure control established in the Core Study was maintained for at least 2 years during treatment with adjunctive perampanel up to 12 mg/day in patients (aged ≥ 12 years) with inadequately controlled GTC seizures in IGE. Relative to data from the Core Study, perampanel administration was similarly safe and well-tolerated, and the safety profile was consistent with that reported for double-blind, placebo-controlled studies in patients with focal-onset seizures. These data suggest that long-term adjunctive perampanel has a favorable risk-benefit ratio in patients with inadequately controlled GTC seizures.

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CONFLICT OF INTEREST

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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.

STATISTICAL ANALYSIS

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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