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- Patient identifiers within text, tables, or figures
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2 STUDY SYNOPSIS

Name of Company: Eisai Inc. and Eisai Ltd.	INDIVIDUAL STUDY TABLE		(For National Authority Use Only)
Name of Finished Product: Perampanel oral tablet	Referring to Module 5 of the Dossier		
Name of Active Ingredient: Perampanel	Volume:	Page:	
Study Title			
A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures			
Investigators/Sites			
██████████ MD, ██████████ (principal investigator). Multicenter, 78 sites in 16 countries (Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania, Poland, Serbia, South Korea, United States; Appendix 16.1.4 for list of investigators and sites).			
Publication (Reference)			
None			
Study Period			
13 Jul 2011 (date of informed consent for first subject entered into the OLE) to 01 Mar 2014 (interim data cutoff date)			
Phase of Development			
Phase 3			
Objectives			
The purpose of the Extension Phase was to evaluate the long-term safety, tolerability, and efficacy of perampanel in subjects with primary generalized tonic-clonic (PGTC) seizures.			
Methodology			
This interim synoptic report presents all data available from subjects who entered the Extension Phase of Study E2007-G000-332 (hereafter referred to as Study 332) as of the cutoff date of 01 Mar 2014.			
Subjects who completed the Prerandomization Phase (Screening and Baseline) and the double-blind (DB), placebo-controlled Randomization Phase (4-week Titration and 13-week Maintenance Periods) of Study 332 (ie, Core Study), and who were otherwise eligible, had the option to enter the Extension Phase. The Extension Phase consisted of 2 parts: Part A (6-week blinded Conversion Period + 32-week Maintenance and Part B (maximum of 104 weeks Maintenance). In addition, a 4-week Follow-up Period was to be completed by all subjects after the last on-treatment visit in the Extension Phase. The Extension Phase will be terminated upon commercial availability of perampanel or if a positive risk-benefit assessment in the treatment of PGTC is not demonstrated.			
During the Conversion Period, all subjects and investigators remained blinded to the treatment (perampanel 2 to 8 mg/day or placebo) received in the preceding Core Study. During the Conversion Period, subjects who had been assigned to placebo in the Core Study were started on blinded treatment with perampanel 2 mg/day and were up-titrated weekly in 2-mg increments to the optimal dose per the investigator's discretion. Subjects 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. During the Conversion Period, per the investigators' judgment, the dose of perampanel was decreased in the event of intolerance, and the dose of			

perampanel was increased up to 12 mg if needed for better seizure control, until the optimal dose was found. Subjects whose dose had been decreased could have their dose increased again once tolerability had improved.

During the Maintenance Period of the Extension Phase, subjects were unblinded to study treatment and remained on the optimal perampanel dose established during the blinded Conversion Period. Dose adjustment during 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 subjects who did not tolerate a minimum dose of 2 mg/day during the Extension Period were discontinued from the study. The maximum dose of perampanel allowed during the Extension Phase was 12 mg/day.

Subjects entered the Extension Phase on the same concomitant antiepileptic drugs (AEDs) they were receiving at the end of the Core Study. During the Maintenance Period of the Extension Phase, changes to concomitant AED(s) (addition, deletion, or dose adjustment) were allowed, with care taken when switching between an inducer and non-inducer AED.

Participation in Part B of the Extension Phase was dependent upon the subject's total number of weeks of exposure to perampanel and the timing of Part A completion relative to the Core Study data review. Subjects who elected to participate in Part B were treated until they had at least 52 weeks of total exposure to perampanel in the study. If a positive risk-benefit assessment in the treatment of PGTC seizures was demonstrated, subjects 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, subjects ended treatment under this protocol and continued to the Follow-up Period of the Extension Phase. Subjects who elected not to participate in Part B ended treatment in this study and continued to the Follow-up Period of the Extension Phase.

Additional details concerning the Extension Phase of Study 332 are provided in Appendix 3 of the protocol ([Appendix 16.1.1](#)).

Number of Subjects (Planned and Enrolled)

Planned: Up to 164 subjects from the Core Study. Enrolled in Extension Phase at data cutoff date: 114 subjects, including 56 subjects who had been assigned to perampanel arm in Core Study and 58 subjects who had been assigned to placebo arm in Core Study. Treated in open-label extension study at data cutoff date: 114 subjects.

Diagnosis and Main Criteria for Inclusion

Male and female subjects were eligible to participate in the Extension Phase if they completed Visit 8 of the Core Study, continued to be treated with a stable dose of 1 to a maximum of 3 approved AEDs; were able to record seizure information in diaries and report adverse events (AEs) (or had a legal guardian who was able to perform these duties); and for females of childbearing potential, had a negative urine pregnancy test at Visit 8 of Core Study and were willing to commit to the consistent and correct use of a medically-acceptable method of contraception for the duration of the study and for at least 30 days after administration of the last dose of study drug.

Test Treatment, Dose, Mode of Administration, and Batch Numbers

Perampanel was supplied as 2-mg or 4-mg oral tablets (batch numbers were: [REDACTED])

Treatment Schedule:

All doses were taken once daily, by mouth, before bedtime, and with food.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Placebo oral tablets matching perampanel 2-mg oral tablets (batch numbers were: [REDACTED])

Duration of Treatment

The planned total duration of perampanel treatment during the Extension Phase was a minimum of 52 weeks up to a maximum of 142 weeks (38 weeks in Part A + 104 weeks in Part B).

Assessments

The schedule of assessments for the Extension Phase is provided in Appendix 3 of the protocol ([Appendix 16.1.1](#)).

Efficacy Assessments

Efficacy assessments included seizure counts from subject diaries.

Safety

Safety was assessed during the Extension Phase by monitoring AEs, treatment discontinuation, suicidal ideation and behavior (Columbia Suicide Severity Rating Scale [C-SSRS]), prior and concomitant medication usage, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, and changes in physical and neurological examinations. In addition, a withdrawal questionnaire was administered to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel.

Statistical Methods

Details concerning the data analyses are specified in the Statistical Analysis Plan (SAP) provided in [Appendix 16.1.9](#). Efficacy analyses were based on the Full Analysis Set (FAS), which comprised all subjects who were eligible to participate in the Extension Phase, received at least 1 dose of perampanel in this phase, and had baseline seizure frequency data and at least 1 observation of valid seizure diary data during the perampanel treatment duration. Safety analyses were based on the Safety Analysis Set, defined as subjects who received at least 1 dose of perampanel in the Extension Phase and had any on-therapy safety data during this phase.

All data analyses were descriptive in nature, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints.

The key efficacy endpoints included the percent change in seizure frequency (PGTC and all seizures types) per 28 days during treatment relative to baseline as well as the proportion of subjects who experienced a 50% or greater reduction in PGTC and total seizure frequency during treatment per 28 days relative to baseline (responder). Two general approaches were used to analyze efficacy data. The first examined seizure data during the perampanel treatment duration and used the Pre-perampanel Baseline for evaluating change. The second approach examined seizure data as a function of randomized treatment group in the Core Study and used the Prerandomization Phase of the Core Study as the baseline for evaluating change.

The Pre-perampanel Baseline was defined as follows: (1) for subjects who had been assigned to placebo treatment in the Core Study, the Pre-perampanel Baseline was computed from all valid seizure diary data during the Core Study, and (2) for subjects who had been assigned to perampanel in the Core Study, the Pre-perampanel Baseline was computed from all valid seizure diary data during the Prerandomization Phase plus the 4 weeks prior to the Prerandomization Phase of the Core Study. For all efficacy analyses, the perampanel treatment duration consisted of: (1) the Randomization Phase of the Core Study plus the Extension Phase for subjects assigned to perampanel in the Core Study, and (2) the Extension Phase for subjects assigned to placebo in the Core Study.

For analyses using the Prerandomization Phase of the Core Study for determining baseline seizure frequency, efficacy data were summarized by randomized, DB treatment group for the Core Study periods (Titration, Maintenance) and Extension Phase periods (Conversion Period and by 13-week intervals in Maintenance Period).

Efficacy endpoints, and their analyses, are defined in the SAP, located in [Appendix 16.1.9](#).

Safety data were summarized by modal perampanel dose (less than 4 mg/day, 4 mg/day, greater than 4 to 8 mg/day, greater than 8 to 12 mg/day), as well as for the total subjects and included data from the entire perampanel treatment duration, defined as all exposure to perampanel in the Core Study or Core Study + Extension Phase. Summaries of AEs were limited to treatment-emergent AEs (TEAE), defined as an AE that

either began on or after the date of first dose of perampanel and up to 30 days after the last dose of perampanel, re-emerged during treatment after having been present at Baseline but stopped before treatment, or began before the date of first perampanel dose and worsened in severity during the perampanel treatment. AEs were classified into standardized terminology from the verbatim description (investigator term) according to the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary, version 16.1. TEAEs were summarized by System Organ Class (SOC) and MedDRA preferred term. The following prespecified categories of TEAEs of special interest were also summarized: suicidal ideation and behavior, abuse potential; alertness and cognition; hostility/aggression; psychosis and psychotic disorder, status epilepticus/convulsions; drug-related hepatic disorder abnormalities; cardiac and electrocardiogram (ECG) TEAEs; rash; fall; and accident/injury; standardized MedDRA queries (SMQ) were used to identify relevant terms for most categories. Laboratory results were summarized using Système International (SI) units, as appropriate. Additional details on safety endpoints and their analyses are described in the SAP, located in [Appendix 16.1.9](#).

Changes in the Conduct of the Study or Planned Analyses

There were 3 global amendments to the original protocol. Changes made to the protocol following each amendment are detailed in [Appendix 16.1.1](#). There were no changes to the planned analyses of data for the Extension Phase. The details around imputation of seizure data after Visit 15 were not included in the SAP. From Visit 15 the seizure diary was completed only for days on which a seizure occurred. Therefore, during this period, days with no entry in the seizure diary were imputed with 'no seizures.' For purposes of the analysis, zero was imputed for non-seizure days. For the same reason, diary compliance is only derived up to Visit 15.

As there was no Per Protocol Population, there were no prespecified criteria defined in the SAP for protocol deviations in the Extension Phase.

Results

Subject Disposition/Analysis Sets

In total, 140 subjects completed the Core Study and were eligible to enter the Extension Phase. Of these, 114 subjects entered the Extension Phase (58 placebo, 56 perampanel) as of the cutoff date for this report ([Table 14.1.1.2.2](#)), representing 81.4% of the 140 subjects who completed the Core Study ([Table 14.1.1.3](#) of the Core Study). All 114 subjects in the Extension Phase received at least 1 dose of perampanel and were included in the Safety Analysis Set.

[Table 1](#) summarizes subject disposition in the Extension Phase for the Safety Analysis Set based upon the End of Study (Subject Disposition) case report form (CRF). As of the interim data cutoff date, 16 of the 114 subjects (14.0%) in the Safety Analysis Set had been discontinued from the Extension Phase, and 97 subjects (85.1%) remained ongoing in the Extension Phase. One subject had completed the Extension Phase as of the cutoff date for this report. The most common primary reasons for discontinuation of perampanel treatment in the Extension Phase were AE (6.1%), inadequate therapeutic effect (3.5%), and subject choice (2.6%) ([Table 14.1.1.2.1](#)). Secondary reasons for discontinuation from the Extension Phase are summarized for the Safety Analysis Set in [Table 14.1.1.3.1](#).

In the Extension Phase, 73.7% of subjects have a modal daily perampanel dose of greater than 4 to 8 mg/day and 16.7% had a modal daily dose of greater than 8 to 12 mg/day ([Table 14.1.1.3.1](#)).

Table 1 Subject Disposition and Primary Reason for Discontinuation from Study by Modal Daily Perampanel Dose – Extension Phase: Safety Analysis Set

Category	Modal Daily Perampanel Dose				Total (N=114)
	<4 mg/day (N=4)	4 mg/day (N=7)	>4 to 8 mg/day (N=84)	>8 to 12 mg/day (N=19)	
Treated, n (%)	4 (100.0)	7 (100.0)	84 (100.0)	19 (100.0)	114 (100.0)
Completed Extension Phase, n (%)	0	0	1 (1.2)	0	1 (0.9)
Discontinued from Extension Phase, n (%)	0	1 (14.3)	10 (11.9)	5 (26.3)	16 (14.0)
Ongoing in Extension Phase, n (%)	4 (100.0)	6 (85.7)	73 (86.9)	14 (73.7)	97 (85.1)
Primary reason for discontinuation ^a , n (%)					
Adverse event	0	1 (14.3)	3 (3.6)	3 (15.8)	7 (6.1)
Lost to follow-up	0	0	0	0	0
Subject choice	0	0	2 (2.4)	1 (5.3)	3 (2.6)
Inadequate therapeutic effect	0	0	4 (4.8)	0	4 (3.5)
Withdrawal of consent	0	0	0	1 (5.3)	1 (0.9)
Pregnancy	0	0	1 (1.2)	0	1 (0.9)
Other	0	0	0	0	0

Percentages are based on the number of subjects enrolled and treated in the relevant treatment group.

a: As reported on the Subject Disposition Extension Phase CRF.

CRF = case report form, N = total number of subjects, n = number of subjects with characteristic

Source: [Table 14.1.1.2.1](#).

Subject disposition in the Extension Phase among the 114 Enrolled Subjects is summarized by treatment in the Core Study in [Table 14.1.1.2.2](#) (primary reason for discontinuation) and [Table 14.1.1.3.2](#) (secondary reason for discontinuation). The frequency distribution of the primary reasons for discontinuation in the Extension Phase was generally similar for subjects who had received treatment with placebo or perampanel in the Core Study.

The completion and discontinuation rates during the Extension Phase are summarized by period and phase for the Safety Analysis Set and Enrolled Subjects in [Table 14.1.1.4.1](#) and [Table 14.1.1.4.2](#), respectively. The distribution of subjects by country and site are summarized for the Safety Analysis Set in [Table 14.1.1.1.1](#) and for Enrolled Subjects in [Table 14.1.1.1.2](#).

Demographic and Other Baseline Characteristics

The demographic characteristics and epilepsy-specific history at entry into the Core Study are summarized for subjects in the Safety Analysis Set in [Table 2](#). The demographic and baseline epilepsy-specific characteristics for the FAS did not differ as a function of previous treatment in the Core Study with placebo or perampanel ([Table 14.1.4.1.1.2](#)).

Table 2 Demographic and Baseline Characteristics by Modal Daily Perampanel Dose – Extension Phase: Safety Analysis Set

Category	Modal Daily Perampanel Dose				Total (N=114)
	<4 mg/day (N=4)	4 mg/day (N=7)	>4 to 8 mg/day (N=84)	>8 to 12 mg/day (N=19)	
Age (Year)					
Mean (SD)	20.8 (2.06)	31.6 (13.97)	27.4 (10.98)	27.1 (11.83)	27.4 (11.14)
Min, Max	18, 23	14, 50	13, 70	12, 58	12, 70
Age Group, n (%)					
<17	0	1 (14.3)	10 (11.9)	3 (15.8)	14 (12.3)
≥17 to <65 years	4 (100.0)	6 (85.7)	73 (86.9)	16 (84.2)	99 (86.8)
≥65	0	0	1 (1.2)	0	1 (0.9)
<18	0	1 (14.3)	13 (15.5)	3 (15.8)	17 (14.9)
≥18 to <65 years	4 (100.0)	6 (85.7)	70 (83.3)	16 (84.2)	96 (84.2)
≥65	0	0	1 (1.2)	0	1 (0.9)
Sex, n (%)					
Male	3 (75.0)	3 (42.9)	35 (41.7)	9 (47.4)	50 (43.9)
Female	1 (25.0)	4 (57.1)	49 (58.3)	10 (52.6)	64 (56.1)
Race, n (%)					
White	1 (25.0)	3 (42.9)	38 (45.2)	16 (84.2)	58 (50.9)
Black or African American	0	0	2 (2.4)	1 (5.3)	3 (2.6)
Asian	3 (75.0)	4 (57.1)	43 (51.2)	2 (10.5)	52 (45.6)
Other	0	0	1 (1.2)	0	1 (0.9)
Seizure Type ^a , n (%)					
Tonic-clonic	4 (100.0)	7 (100.0)	84 (100.0)	19 (100.0)	114 (100.0)
Myoclonic	2 (50.0)	4 (57.1)	32 (38.1)	10 (52.6)	48 (42.1)
Absence	1 (25.0)	4 (57.1)	35 (41.7)	17 (89.5)	57 (50.0)
Clonic	0	0	1 (1.2)	0	1 (0.9)
Tonic	1 (25.0)	0	1 (1.2)	0	2 (1.8)
Atonic	0	0	0	0	0
Time since Diagnosis (y) ^a					
Mean (SD)	10.479 (4.3037)	18.881 (12.9080)	16.643 (11.7710)	17.486 (12.5281)	16.705 (11.7424)
Min, Max	6.65, 16.63	4.97, 41.52	1.03, 57.09	1.91, 53.05	1.03, 57.09

Percentages based on the total number of subjects with non-missing values in the relevant treatment group.

Age at informed consent in Core Study. All other demographic characteristics are as of baseline of the Core Study.

Max = maximum, Min = minimum, N = total number of subjects, n = number of subjects with characteristic, SD = standard deviation, y = year.

a: Time from diagnosis and history of seizure type(s) are with respect to date of informed consent in Core Study.

If the day or month of diagnosis was missing, the day was imputed to be the 1st of the month and the month was imputed to be January. If imputed date was before the birth date, the birth date was used in place of date of diagnosis.

Source: [Table 14.1.4.1.1.1](#).

Concomitant Medications

The number of AEDs taken at Core Study baseline is summarized in [Table 14.1.4.2.1](#) for the Safety Analysis Set, while the use of specific AEDs at Core Study baseline is summarized for this analysis set in [Table 14.1.4.2.2](#). In total, 36.8% of subjects in the Safety Analysis Set were taking 1 AED, 47.4% were taking 2 AEDs, and 15.8% were taking 3 AEDs at Core Study baseline, and the most common AEDs taken were lamotrigine (40.4%), valproic acid (32.5%), levetiracetam (27.2%), topiramate (14.9%), ergenyl chrono (10.5%), and zonisamide (10.5%); all other background AEDs were taken by less than 10% of subjects. Of note, 11 subjects (9.6%) were taking carbamazepine, 7 (6.1%) were taking phenytoin, and 5 (4.4%) were taking oxcarbazepine during the Extension Phase.

A summary of all concomitant medications, including AED(s) by Anatomic Therapeutic Class, taken during the Extension Phase, is presented in [Table 14.1.4.3.1](#) for the Safety Analysis Set.

Treatment and Diary Compliance

Diary compliance was ascertained from the days on which valid seizure counts were recorded in the subject diary, and the mean compliance for the combined total was 98.0% across the Extension Phase for the FAS ([Table 14.1.6.1](#)). Treatment compliance, ascertained from counts of tablets dispensed and tablets returned, averaged approximately 98.2% across the entire Extension Phase (mean of 97.7% for blinded Conversion Period and 100.0% for Maintenance Period) for the FAS ([Table 14.1.5.2](#)). Study medication compliance is summarized by visit in the Extension Phase for the FAS in [Table 14.1.5.1](#).

Efficacy

Efficacy Relative to Pre-perampanel Baseline

The percent change in seizure frequency per 28 days relative to the Pre-perampanel Baseline and the seizure frequency per 28 days are summarized for each 13-week interval of the entire perampanel treatment duration (Core Study and Extension Phase) through Weeks 105 to 117 for the FAS in [Table 14.2.1.1.1.1](#) and [Table 14.2.1.1.1.2](#), respectively. In each display, observed data are summarized for PGTC and all seizures. Summaries of the percent change in seizure (PGTC and all seizures) frequency per 28 days relative to the Pre-perampanel Baseline and the seizure frequency per 28 days by 13-week interval of perampanel treatment duration are provided for those subsets of the FAS with at least 13 weeks of treatment ([Table 14.2.1.1.1.3](#) and [Table 14.2.1.1.1.4](#)), at least 26 weeks of treatment ([Table 14.2.1.1.1.5](#) and [Table 14.2.1.1.1.6](#)), at least 39 weeks of treatment ([Table 14.2.1.1.1.7](#) and [Table 14.2.1.1.1.8](#)), at least 1 year of treatment ([Table 14.2.1.1.1.9](#) and [Table 14.2.1.1.1.10](#)), and at least 2 years of treatment ([Table 14.2.1.1.1.11](#) and [Table 14.2.1.1.1.12](#)).

[Table 3](#) summarizes the median percent change from the Pre-perampanel Baseline in seizure frequency per 28 days by 13-week interval through Weeks 92 to 104 (end of Year 2); data are shown for PGTC seizures and all seizures. These data indicate that the benefit of perampanel is sustained over time, although it should be noted that the number of subjects with available data declined over time. The change in the percent reduction in the frequency of PGTC seizures during the first 3 to 6 months following initiation of adjunctive perampanel treatment is maintained for approximately 2 years. Plots of the median percent change in PGTC seizures per 28 days by 13-week interval is plotted in [Figure 1](#) for the subsets of subjects in the FAS who received at least 26 weeks, 39 weeks, 1 year, and 2 years of treatment. A similar plot is provided for all seizures in [Figure 14.2.2.1.1.1](#). [Figure 2](#) displays the 50% responder rate from Pre-perampanel Baseline in PGTC seizures per 28 days by 13-week interval for the subsets of subjects in the FAS who received at least 26 weeks, 39 weeks, 1 year, and 2 years of treatment. A similar plot is provided for all seizures in [Figure 14.2.2.1.2.1](#).

Summaries of the percentage of responders in the FAS (ie, 50% or more decrease in seizure frequency per 28 days) based on the Pre-perampanel Baseline are provided by 13-week interval for the entire perampanel treatment duration in [Table 14.2.1.1.2.1](#), and for those subsets of the FAS with at least 13 weeks of treatment ([Table 14.2.1.1.2.2](#)), at least 26 weeks of treatment ([Table 14.2.1.1.2.3](#)), at least 39 weeks of treatment ([Table 14.2.1.1.2.4](#)), at least 1 year of treatment ([Table 14.2.1.1.2.5](#)), and at least 2 years of treatment ([Table 14.2.1.1.2.6](#)). In each display, observed data are summarized for PGTC and all seizures.

[Table 3](#) additionally summarizes the responder rate by 13-week interval through Weeks 92 to 104 (end of Year 2) for PGTC seizures and all seizures for the FAS. These data were consistent with those for percent change in seizure frequency and showed that the responder rate was generally stable across time from about Week 26 through the end of Year 2. Plots of median percent change in seizure frequency by 13-week interval among the subsets of subjects in the FAS who received at least 26 weeks, 39 weeks, 1 year, and 2 years of treatment are provided in [Figure 14.2.1.1.1.1](#) based on PGTC seizures and in [Figure 14.2.2.1.1.1](#) for all seizures. Plots of responder rate by 13-week interval among the subsets of subjects in the FAS who received at least 26 weeks, 39 weeks, 1 year, and 2 years of treatment are provided in [Figure 14.2.1.1.2.1](#) based on PGTC seizures and in [Figure 14.2.2.1.2.1](#) for all seizures.

Table 3 Summary of Percent Change from Pre-perampanel Baseline in Seizure Frequency per 28 Days and Responder Analysis During Perampanel Treatment Duration – Extension Phase: Full Analysis Set

Analysis window/ Statistic	Seizure Type	
	PGTC Seizures	All Seizures
Pre-perampanel – n	114	114
Median seizure frequency	2.39	4.64
Perampanel Treatment Duration		
Weeks 1-13 – n	114	114
Median % change	-84.29	-57.15
Responder rate, n (%)	78 (68.4)	62 (54.4)
Weeks 14-26 – n	94	94
Median % change	-71.20	-63.69
Responder rate, n (%)	67 (71.3)	61 (64.9)
Weeks 27-39 – n	68	68
Median % change	-78.95	-76.33
Responder rate, n (%)	47 (69.1)	45 (66.2)
Weeks 40-52 – n	44	44
Median % change	-81.74	-83.80
Responder rate, n (%)	29 (65.9)	33 (75.0)
Weeks 53-65 – n	34	34
Median % change	-100.00	-90.65
Responder rate, n (%)	27 (79.4)	31 (91.2)
Weeks 66-78 – n	11	11
Median % change	-100.00	-80.46
Responder rate, n (%)	10 (90.9)	9 (81.8)
Weeks 79-91 – n	9	9
Median % change	-100.00	-82.05
Responder rate, n (%)	9 (100.0)	9 (100.0)
Weeks 92-104 – n	1	1
Median % change	-100.00	-83.64
Responder rate, n (%)	1 (100.0)	1 (100.0)

Week 1 begins on the date of first dose of perampanel treatment duration. The perampanel treatment duration starts from the first perampanel dose in the Core Study or Extension Phase and continues to and includes the date of the last dose of perampanel in the Extension Phase. In Part B of the Extension Phase (after Visit 15), the seizure diary was only completed for days on which a seizure occurred. For purposes of the analysis, zero was imputed for non-seizure days. For any given analysis window and seizure type(s), a 50% responder from pre-perampanel is a subject whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than the pre-perampanel baseline seizure frequency per 28 days for that same seizure type(s).

n = number of subjects with event, PGTC = primary generalized tonic-clonic.

Source: [Table 14.2.1.1.1.1](#) and [Table 14.2.1.1.2.1](#).

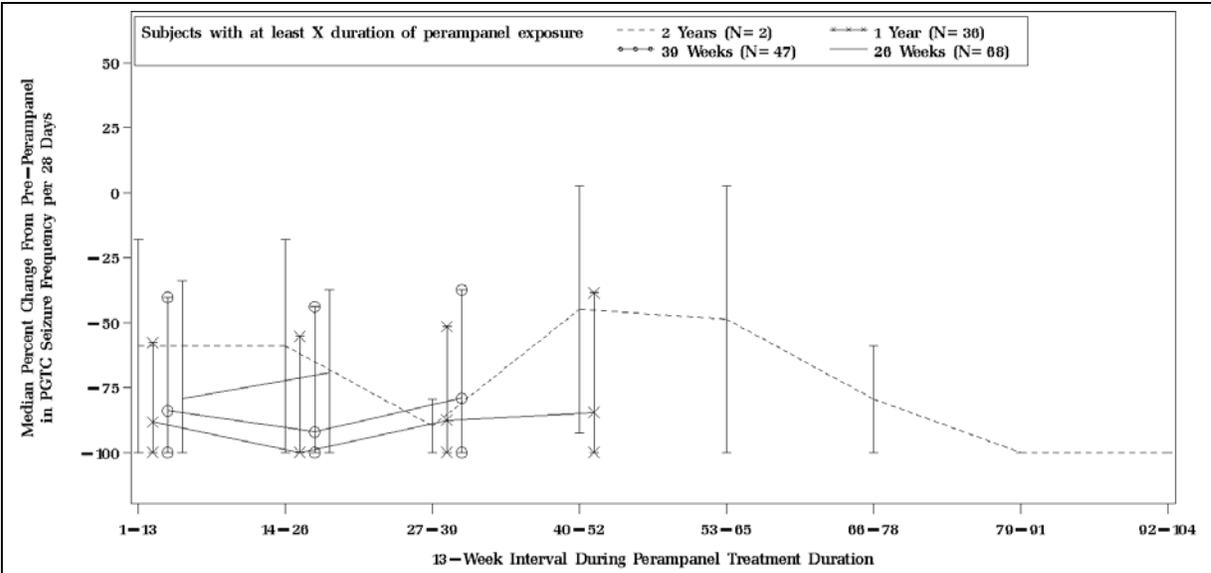


Figure 1 Median Percent Change from Pre-perampanel Baseline in PGTC Seizure Frequency per 28 Days by 13-week Interval During Perampanel Treatment Duration – Extension Phase: Full Analysis Set

PGTC = primary generalized tonic-clonic.
 Source: [Figure 14.2.1.1.1.1](#).

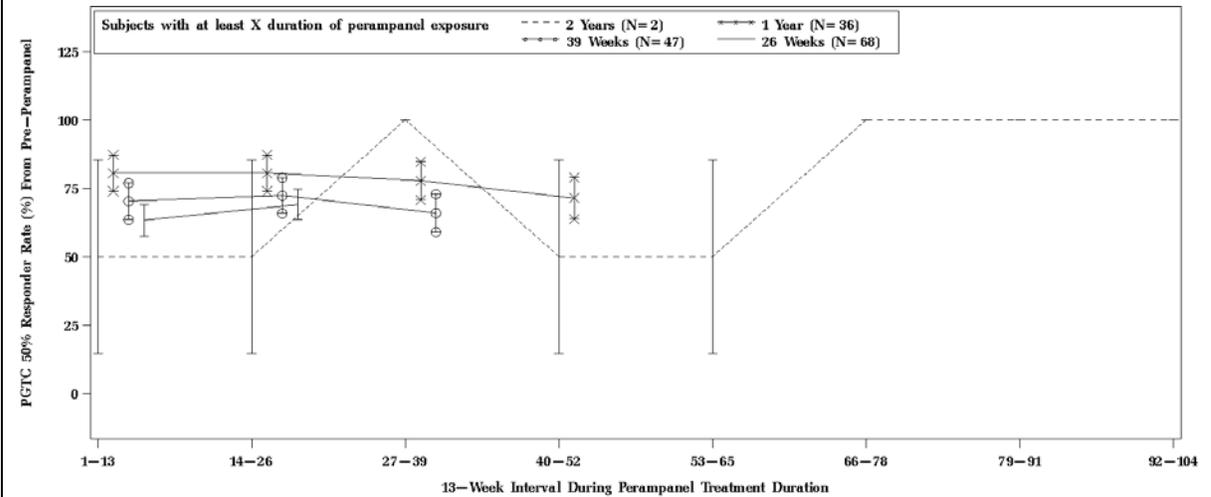


Figure 2 50% Responder Rate from Pre-perampanel Baseline in PGTC Seizure Frequency per 28 Days by 13-week Interval During Perampanel Treatment Duration – Extension Phase: Full Analysis Set

PGTC = primary generalized tonic-clonic.
 Source: [Figure 14.2.1.1.2.1](#).

The cumulative percent change from Pre-perampanel Baseline in PGTC seizure frequency, categorized in 25% increments, during various minimum durations of perampanel exposure (1 day, 13, 26, and 39 weeks, 1 and 2 years) is summarized for the FAS in [Table 14.2.1.1.3.1](#). During each 13-week period of the first year of perampanel treatment, the proportion of subjects who achieved a 100% reduction in PGTC seizures is at least 35% (range: 35.3% at 1 to 13 weeks to 58.3% at 14 to 26 weeks) in each exposure group. During the second year of perampanel treatment, the proportions of subjects who achieved a 100% reduction in PGTC seizures increases further (range: 50.0% to 100.0%), although the number of subjects exposed becomes quite small. The cumulative percent change from Pre-perampanel Baseline in all seizures seizure frequency, categorized in 25% increments, during various minimum durations of perampanel exposure (1 day, 13, 26, and 39 weeks, 1 and 2 years) is summarized for the FAS in [Table 14.2.1.2.3.1](#).

Subgroup Analyses. Subgroup analyses of the percent change in PGTC seizure frequency per 28 days and PGTC seizure frequency relative to the Pre-perampanel Baseline by 13-week interval for the entire perampanel treatment duration are provided for the FAS by age in [Table 14.2.1.1.1.13](#) and [Table 14.2.1.1.1.14](#) (Age Group 1: ≥ 12 to < 17 , ≥ 17 to < 65 , ≥ 65) and in [Table 14.2.1.1.1.15](#) and [Table 14.2.1.1.1.16](#) (Age Group 2: ≥ 12 to < 18 , ≥ 18 to < 65 , ≥ 65); by sex in [Table 14.2.1.1.1.17](#) and [Table 14.2.1.1.1.18](#); by race in [Table 14.2.1.1.1.19](#) and [Table 14.2.1.1.1.20](#); and by number of AEDs at Core Study baseline in [Table 14.2.1.1.1.21](#) and [Table 14.2.1.1.1.22](#). The responder rate for PGTC seizures is summarized by 13-week interval for the entire perampanel treatment duration for the FAS by age in [Table 14.2.1.1.2.7](#) (Age Group 1) and [Table 14.2.1.1.2.8](#) (Age Group 2); by sex in [Table 14.2.1.1.2.9](#); by race in [Table 14.2.1.1.2.10](#); and by number of background AEDs at Core Study baseline in [Table 14.2.1.1.2.11](#).

Data for age, sex, and race subgroups were generally consistent with those for the overall population in showing a similar stable pattern over time of improvement in PGTC seizure control as reflected by the median percent change in seizure frequency and responder rate. Improvements in PGTC seizure control were seen in all subgroups based on the number of background AEDs at Core Study baseline.

Subgroup analyses of the percent change in seizure frequency per 28 days and seizure frequency relative to the Pre-perampanel Baseline by 13-week interval for the entire perampanel treatment duration were also done for all seizure types and are provided for the FAS by age in [Table 14.2.1.2.1.1](#) and [Table 14.2.1.2.1.2](#) (Age Group 1) and [Table 14.2.1.2.1.3](#) and [Table 14.2.1.2.1.4](#) (Age Group 2); by sex in [Table 14.2.1.2.1.5](#) and [Table 14.2.1.2.1.6](#); by race in [Table 14.2.1.2.1.7](#) and [Table 14.2.1.2.1.8](#); and by number of background AEDs at Core Study baseline in [Table 14.2.1.2.1.9](#) and [Table 14.2.1.2.1.10](#). The responder rates for all seizure types are summarized by 13-week interval for the entire perampanel treatment duration for the FAS by age in [Table 14.2.1.2.2.1](#) (Age Group 1) and [Table 14.2.1.2.2.2](#) (Age Group 2); by sex in [Table 14.2.1.2.2.3](#); by race in [Table 14.2.1.2.2.4](#); and by number of background AEDs at Core Study baseline in [Table 14.2.1.2.2.5](#).

Efficacy Relative to Core Study Prerandomization Phase

The percent change in PGTC seizure frequency per 28 days relative to the Core Study Prerandomization Phase, and summary statistics regarding seizure frequency, are summarized by previous DB treatment for each period/phase of the Core Study and Extension Phase for the FAS in [Table 14.2.2.1.1.1](#) and [Table 14.2.2.1.1.2](#), respectively. Similarly, summary tables for the percent change in seizure frequency and seizure frequency per 28 days are provided for all seizures in [Table 14.2.2.2.1.1](#) and [Table 14.2.2.2.1.2](#), respectively. Plots of the median percent change from Prerandomization Phase in PGTC and all seizure frequency per 28 days for each period/phase of the Core Study and Extension Phase are provided for the FAS in [Figure 14.2.1.2.1.1](#) and [Figure 14.2.2.2.1.1](#), respectively.

The percentage of responders in the FAS based on Core Study Prerandomization Phase are summarized by prior DB treatment group for each period/phase of the Core Study and Extension Phase in [Table 14.2.2.1.2.1](#) (PGTC seizures) and [Table 14.2.2.2.2.1](#) (all seizures). By the end of the blinded Conversion Period of the Extension Phase, subjects who had received prior DB treatment with placebo showed similar efficacy as subjects who received previous DB treatment with perampanel. Plots of the responder rate for PGTC seizures and all seizures (using Prerandomization Phase as baseline) for each period/phase of the Core Study and Extension Phase are provided for the FAS in [Figure 14.2.1.2.2.1](#) and [Figure 14.2.2.2.2.1](#), respectively.

[Table 4](#) summarizes, by previous DB treatment group (placebo or perampanel), the median percent change in PGTC seizure frequency per 28 days and the percentage of PGTC responders for the Core Study Maintenance Period (when dose was stable), the blinded Conversion Period of the Extension Phase, and by 13-week intervals through Weeks 79 to 91 for the Maintenance Period of the Extension Phase. Among subjects who received prior

DB treatment with placebo, both the median percent reduction in PGTC seizure frequency and the responder rate increased to a level similar to that for subjects receiving previous DB treatment with perampanel by the end of the blinded Conversion Period of the Extension Phase.

The median percent change in seizure frequency indicates efficacy established in the Core Study was maintained during the Extension Phase.

Table 4 Percent Change from Core Study Prerandomization Phase in PGTC Seizure Frequency per 28 days and Responder Rate – Extension Phase: Full Analysis Set

Analysis Window Parameter	Median Percent Change in Total Seizure Frequency		Responder Rate (n, %)	
	Prior Placebo	Prior Perampanel	Prior Placebo	Prior Perampanel
Seizure Freq. – Prerandomization Phase, n	58	56	58	56
Median	2.50	2.50		
Core Study Maintenance Period, n	58	56	58	56
Median % change or responder rate, n (%)	-41.68	-85.87	23 (39.7)	38 (67.9)
Extension Conversion Period, n	58	56	58	56
Median % change or responder rate, n (%)	-100.00	-100.00	42 (72.4)	42 (75.0)
Extension Maintenance Weeks 1-13, n	47	45	47	45
Median % change or responder rate, n (%)	-79.49	-82.42	34 (72.3)	33 (73.3)
Extension Maintenance Weeks 14-26, n	29	34	29	34
Median % change or responder rate, n (%)	-69.23	-85.91	20 (69.0)	28 (82.4)
Extension Maintenance Weeks 27-39, n	20	27	20	27
Median % change or responder rate, n (%)	-83.52	-100.00	14 (70.0)	19 (70.4)
Extension Maintenance Weeks 40-52, n	9	8	9	8
Median % change or responder rate, n (%)	-100.00	-100.00	6 (66.7)	8 (100.0)
Extension Maintenance Weeks 53-65, n	9	8	9	8
Median % change or responder rate, n (%)	-100.00	-100.00	8 (88.9)	7 (87.5)
Extension Maintenance Weeks 66-78, n	1	2	1	2
Median % change or responder rate, n (%)	-17.95	-100.00	0	2 (100.0)
Extension Maintenance Weeks 79-91, n	1	1	1	1
Median % change or responder rate, n (%)	-100.00	-100.00	1 (100.0)	1 (100.0)

Extension Maintenance Week 1 begins on the date of first dose of the perampanel treatment duration, which starts on the date of the first dose of perampanel in either the Core Study or Extension Phase and continues to and includes the date of the last dose of perampanel in the Extension Phase. In Part B of the Extension Phase (after Visit 15), the seizure diary is only completed for days on which a seizure occurred. For purposes of the analysis, zero was imputed as non-seizure days.

For any given analysis window and seizure type(s), a 50% responder from Core Study Prerandomization is a subject whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than the Core Study Prerandomization baseline seizure frequency per 28 days for that same seizure type(s).

freq = frequency, PGTC = primary generalized tonic-clonic, n = number of subjects with event.

Source: [Table 14.2.2.1.1.1](#) and [Table 14.2.2.1.2.1](#).

The cumulative percent change in PGTC seizure frequency from Core Study Prerandomization, categorized in 25% increments, during various minimum durations of perampanel exposure (1 day, 13, 26, and 39 weeks, 1 and 2 years) is summarized by DB treatment group for the FAS in [Table 14.2.2.1.3.1](#). A similar display is provided for the cumulative percent change in all seizures in [Table 14.2.2.2.3.1](#). In the Core Study Maintenance Period, the proportions of subjects who achieved a 100% reduction in PGTC seizures was 12.1% of subjects treated with placebo and 41.1% of subjects treated with perampanel. During each 13-week period of the first year of

perampanel treatment in the Extension Phase Maintenance Period, the proportions of subjects who achieved a 100% reduction in PGTC seizures ranged from 34.5% to 55.6% of subjects treated with placebo and from 38.2% to 62.5% of subjects treated with perampanel. During the second year of perampanel treatment, the proportion of subjects who achieved a 100% reduction in PGTC seizures increased further, although the number of subjects exposed was small.

Subgroup Analyses. Subgroup analyses of the percent change in PGTC seizure frequency per 28 days and PGTC seizure frequency per 28 days relative to the Prerandomization Phase for each period/phase of the Core Study and Extension Phase are provided for the FAS by age in [Table 14.2.2.1.1.3](#) and [Table 14.2.2.1.1.4](#) (Age Group 1) and [Table 14.2.2.1.1.5](#) and [Table 14.2.2.1.1.6](#) (Age Group 2); by sex in [Table 14.2.2.1.1.7](#) and [Table 14.2.2.1.1.8](#); by race in [Table 14.2.2.1.1.9](#) and [Table 14.2.2.1.1.10](#); and by number of AEDs at Core Study baseline in [Table 14.2.2.1.1.11](#) and [Table 14.2.2.1.1.12](#). The responder rate for PGTC seizures (based on Prerandomization Phase) is summarized for each period/phase of the Core Study and Extension Phase for the FAS by age in [Table 14.2.2.1.2.2](#) (Age Group 1) and [Table 14.2.2.1.2.3](#) (Age Group 2); by sex in [Table 14.2.2.1.2.4](#); by race in [Table 14.2.2.1.2.5](#); and by number of background AEDs at Core Study baseline in [Table 14.2.2.1.2.6](#).

Because these subgroup analyses were done by DB treatment group, the number of subjects was small (less than 10) for some of the subgroups. Results were generally consistent for all subgroups in showing improvements in PGTC seizure control following initiation of perampanel therapy in the Extension Phase for subjects who received DB placebo, and sustained improvements in seizure control during the Extension Phase for subjects who had received DB perampanel.

Subgroup analyses of the percent change in seizure frequency per 28 days and seizure frequency relative to the Prerandomization Phase by 13-week interval for each period/phase of the Core Study and Extension Phase were also done for all seizures and are provided for the FAS by age in [Table 14.2.2.2.1.3](#) and [Table 14.2.2.2.1.4](#) (Age Group 1) and [Table 14.2.2.2.1.5](#) and [Table 14.2.2.2.1.6](#) (Age Group 2); by sex in [Table 14.2.2.2.1.7](#) and [Table 14.2.2.2.1.8](#); by race in [Table 14.2.2.2.1.9](#) and [Table 14.2.2.2.1.10](#); and by number of background AEDs at Core Study Prerandomization in [Table 14.2.2.2.1.11](#) and [Table 14.2.2.2.1.12](#).

The responder rates for all seizure types are summarized by 13-week interval for the Prerandomization Phase for each period/phase of the Core Study and Extension Phase and are provided by age in [Table 14.2.2.2.2.2](#) (Age Group 1) and [Table 14.2.2.2.2.3](#) (Age Group 2); by sex in [Table 14.2.2.2.2.4](#); by race in [Table 14.2.2.2.2.5](#); and by number of background AEDs at Core Study Prerandomization in [Table 14.2.2.2.2.6](#).

Safety

Extent of Exposure to Perampanel

The cumulative extent of exposure to perampanel over the Core Study and Extension Phase is summarized by the modal daily dose for the Safety Analysis Set in [Table 14.3.1.1.1](#). The mean \pm SD duration of exposure was 40.34 \pm 28.1 weeks (range: 0.7, 123.7), and 31.6% of subjects in the Safety Analysis Set received more than 52 weeks of perampanel treatment. The total exposure to perampanel was 4,598.4 subject-weeks.

The mean modal dose \pm SD of perampanel across the Extension Phase was 7.6 \pm 1.9 mg/day (range: 2, 12) for the Safety Analysis Set. The mean modal dose \pm SD during the Extension Phase Conversion Period was 6.8 \pm 1.6 mg/day (range: 2, 11) and for the Extension Phase Maintenance Period it was 8.3 \pm 1.9 mg/day (range: 4, 12) ([Table 14.3.1.1.2](#)). It should be noted that the mean dose during the conversion period was less than that during maintenance as half the subjects were up-titrating during that time. The mean dose across the entire perampanel treatment duration (7.4 \pm 1.7 mg/day) was less than that for the Extension Phase since it included data from the Core Study where the maximum dose was targeted at 8 mg/day.

Adverse Events

Overview of Adverse Events

[Table 5](#) summarizes the overall TEAE profile for the Safety Analysis Set. TEAEs included those AEs that occurred from the first day of perampanel administration (in Core Study or Extension 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. A detailed narrative is provided in [Section 14.3.3](#) for each subject who died, had a serious adverse event (SAE) (including symptomatic overdose), had an event considered clinically important by the investigator or the sponsor (eg, falls), or had other events considered to be significant (eg, pregnancies).

Table 5 Treatment-Emergent Adverse Event Summary – Extension Phase: Safety Analysis Set

Category	Modal Daily Perampanel Dose				Total (N=114) n (%)
	<4 mg/day (N=4) n (%)	4 mg/day (N=7) n (%)	>4 to 8 mg/day (N=84) n (%)	>8 to 12 mg/day (N=19) n (%)	
TEAEs	3 (75.0)	7 (100.0)	66 (78.6)	16 (84.2)	92 (80.7)
Treatment-related TEAEs ^a	1 (25.0)	7 (100.0)	58 (69.0)	12 (63.2)	78 (68.4)
Severe TEAEs	0	0	4 (4.8)	4 (21.1)	8 (7.0)
Serious TEAEs	0	0	5 (6.0)	3 (15.8)	8 (7.0)
Deaths	0	0	0	1 (5.3)	1 (0.9)
Other Serious AEs	0	0	5 (6.0)	2 (10.5)	7 (6.1)
Life threatening	0	0	1 (1.2)	1 (5.3)	2 (1.8)
Requires inpatient hospitalization or prolongs existing hospitalization	0	0	4 (4.8)	3 (15.8)	7 (6.1)
Persistent or significant disability or incapacity	0	0	0	0	0
Congenital anomaly/ birth defect	0	0	0	0	0
Important medical events	0	0	3 (3.6)	1 (5.3)	4 (3.5)
TEAEs leading to dose adjustment	0	7 (100.0)	20 (23.8)	8 (42.1)	35 (30.7)
Leading to withdrawal	0	1 (14.3)	4 (4.8)	3 (15.8)	8 (7.0)
Leading to dose increase	0	0	1 (1.2)	0	1 (0.9)
Leading to dose reduction	0	6 (85.7)	17 (20.2)	5 (26.3)	28 (24.6)
Leading to dose interruption	0	0	0	1 (5.3)	1 (0.9)

Percentages are based on the total number of subjects in the relevant treatment group.

For each row category, a subject with two or more adverse events in that category is counted only once.

Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the Core Study, the perampanel exposure consisted of the Core Study plus the Extension Phase treatment duration. For subjects who received placebo in the Core Study, perampanel exposure consisted of the Extension Phase treatment duration.

AE = adverse event, N = total number of subjects, n = number of subjects with event, TEAE = Treatment-Emergent Adverse Event: an adverse event is treatment emergent if the adverse event started on or after the Date of First Perampanel Dose and before or on the day of (Date of Last Dose + 30 days) during the Extension Phase.

a: Includes TEAEs considered by the Investigator to be possibly or probably related to study drug or TEAEs with missing causality.

Source: [Table 14.3.1.2.1](#).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths: In addition to the 2 deaths that occurred during the Core Study, there was 1 death during perampanel exposure in the Extension Phase ([Table 14.3.2.1.1](#)) that occurred in a subject who received 6 mg during the Core Study. The death during the Extension Phase occurred 64 days after the last dose. The death was assessed by the investigator as not related to study treatment.

This subject had been receiving 10 mg perampanel. The full narrative for this subject is provided in [Section 14.3.3](#).

Serious adverse events: The highest incidence of SAEs occurred among subjects treated in the top modal dose group (3 subjects, 15.8%), but the sample size was small (N=19 subjects). In the Extension Phase, 8 subjects (7.0%) in the Safety Analysis Set had treatment-emergent SAEs (including fatal events) during perampanel exposure across the Core Study and/or during the Extension Phase. A summary of treatment-emergent SAEs by MedDRA SOC and preferred term and perampanel modal daily dose is provided in [Table 14.3.2.2.1](#), while a summary of treatment-emergent SAEs by MedDRA SOC and preferred term and actual perampanel dose at onset is presented in [Table 14.3.2.2.3](#). A listing by subject of all SAEs (including non-TEAEs) other than death is provided in [Table 14.3.2.2.2](#).

The most common treatment-emergent SAEs (preferred terms) were convulsion (n=2, 1.8%) and suicide attempt (n=2, 1.8%). These TEAEs were considered serious either because they were life threatening (suicide attempt) or involved hospitalization or prolonged hospitalization ([Table 14.3.2.2.2](#)). All non-fatal SAEs had resolved or were resolving as of the interim cutoff date ([Table 14.3.2.2.2](#)).

Of the 8 subjects who had treatment-emergent SAEs (including fatal events) during perampanel exposure in the Extension Phase, 1 subject was on a 6-mg/day dose, 4 were on an 8-mg/day dose, 1 was taking 10 mg/day, 1 was taking 12 mg/day, and 1 was taking 10 mg/day that was increased to 12 mg/day perampanel ([Table 14.3.1.2.1](#) and [Listing 16.2.7.1](#)).

TEAEs leading to discontinuation: TEAEs resulting in discontinuation of perampanel treatment occurred in 8 subjects (7.0%) in the Safety Analysis Set during perampanel exposure in the Extension Phase ([Table 14.3.2.3.1](#)). The 2 events that resulted in discontinuation of at least 2 subjects were (preferred term) dizziness (n=3, 2.6%) and suicide attempt (n=2, 1.8%). The 3 subjects who discontinued because of dizziness were taking 6 mg/day, 8 mg/day, and 12 mg/day perampanel, and the 2 subjects who discontinued because of suicide attempts were taking 8 mg/day and 12 mg/day at the time of the suicide attempt. A listing of subjects with TEAEs that led to study or perampanel withdrawal is provided in [Table 14.3.2.3.2](#).

TEAEs requiring interruption or dose reduction of perampanel: In total, 28 subjects (24.6%) in the Safety Analysis Set had a TEAE that resulted in interruption of study drug or dose adjustment (ie, reduction) during exposure to perampanel across the Core Study and/or Extension Phase ([Table 14.3.2.4.1](#)). The most common of these events (greater than or equal to 2.0% incidence) were dizziness (n=13, 11.4%), somnolence (n=6, 5.3%), and irritability (n=5, 4.4%). Of the 13 subjects who required an interruption or dose reduction due to dizziness, 1 subject was taking 4 mg/day, 5 were taking 6 mg/day, and 7 were taking 8 mg/day. Of the 6 subjects requiring an interruption or dose reduction due to somnolence, 2 were taking 6 mg/day, 2 were taking 8 mg/day, 1 was taking 10 mg/day, and 1 was taking 12 mg/day. Of the 5 subjects requiring an interruption or dose reduction due to irritability, 2 were taking 6 mg/day, 2 were taking 8 mg/day, and 1 was taking 12 mg/day. For most subjects, these TEAEs resolved without sequelae and the subject remained on treatment. A listing of subjects with TEAEs that required interruption or dose adjustment is provided in [Table 14.3.2.4.2](#).

Study drug overdose, misuse, abuse, and medication error: Any AEs associated with overdose, misuse, abuse, or medication error were reported on an SAE form and captured in the pharmacovigilance database. No events associated with overdose, misuse, abuse, or medication error were reported during perampanel exposure in the Core Study and/or Extension Phase ([Tables 14.3.2.5.1](#) and [Table 14.3.2.5.2](#)).

Pregnancy: One pregnancy was reported for a woman in the Safety Analysis Set exposed to perampanel across the Core Study and Extension Phase. [REDACTED]

[REDACTED] The narrative for the subject with the confirmed pregnancy is provided in [Section 14.3.3](#).

Other TEAEs of interest: The following AEs of special interest (generally identified using MedDRA SMQ) were examined for the Safety Analysis Set during exposure to perampanel across the Core Study and/or Extension Phase: 1) TEAEs suggestive of abuse potential (based on terms of interest identified by Controlled Substance Staff [CSS] at FDA), 2) TEAEs related to suicidal ideation and behavior, 3) TEAEs related to alertness or cognition, 4) TEAEs related to hostility and aggression, 5) TEAEs related to psychosis and psychotic disorders, 6) TEAEs related to status epilepticus/convulsions, 7) TEAEs related to drug-related hepatic disorder abnormalities, 8) cardiac and ECG TEAEs, 9) TEAEs related to rash, 10) falls, 11) tendon/ligament rupture, 12) ventricular arrhythmia/cyanosis, 13) pancreatitis, and 14) incarceration.

Falls and postictal events such as confusion/aggression could be inherent features of a seizure(s); therefore, there

is a need to distinguish between events that are associated with seizures and those that are not. When evaluating the frequency of falls in the Phase 3 double-blind studies in partial onset seizures, it was determined that at least 50% of investigator-reported falls in those studies were associated with seizures. Therefore, in the current study, to distinguish seizure-associated events from independent ones, a systematic review of reported events of falls, irritability, aggression, agitation, mood altered, abnormal behavior, and anger was conducted, and queries were sent back to the investigator to establish whether the events were related to a seizure or not.

TEAEs related to abuse potential: No subject reported a TEAE suggestive of abuse potential during perampanel exposure, as identified using the MedDRA SMQ terms (Table 14.3.2.6.2).

TEAEs related to suicidal ideation and behavior: [REDACTED]

[REDACTED] The 2 suicide attempts were serious and resulted in treatment discontinuation; all events resolved (Listing 16.2.7.1). Narratives for subjects with suicidal ideation and behavior-related TEAEs are provided in Section 14.3.3.

TEAEs related to alertness or cognition: TEAEs related to alertness and cognition were reported for 21 subjects (18.4%) during perampanel exposure; the most common of these events (greater than or equal to 2%) was somnolence (n=13, 11.4%), aggression (n=3, 2.6%), and agitation (n=3, 2.6%) (Table 14.3.2.6.3). Of the 13 subjects who had somnolence, 6 were taking 8 mg/day, 2 were taking 10 mg/day, and 1 subject each was taking other doses ranging from 4 mg/day to 12 mg/day. Of the 3 subjects who had aggression, each subject was taking a different dose (range: 6 mg/day to 10 mg/day). Of the 3 subjects with agitation, 2 were taking 8 mg/day and 1 was taking 12 mg/day.

TEAEs related to hostility/aggression: TEAEs related to hostility/aggression were identified during perampanel exposure for 7 subjects (6.1%) using narrow SMQ terms and for 22 subjects (19.3%) using narrow and broad SMQ terms (Table 14.3.2.6.4 and Table 14.3.2.6.5). The most common TEAEs using the narrow SMQ criteria were anger and aggression, each reported by 3 subjects (2.6%), and the most common using the narrow and broad SMQ criteria was irritability, reported by 14 subjects (12.3%). [REDACTED]

[REDACTED] This subject recovered from the SAE, the perampanel dose was not changed, and the subject was not withdrawn from perampanel treatment due to this event. A narrative for the subject who experienced this TEAE related to hostility/aggression during perampanel exposure is provided in Section 14.3.3.

TEAEs related to psychosis and psychotic disorders: TEAEs related to psychosis and psychotic disorders were identified during perampanel exposure for 2 subjects (1.8%) using narrow SMQ terms and for 5 subjects (4.4%) using narrow and broad SMQ terms (Table 14.3.2.6.6 and Table 14.3.2.6.7). No event occurred in more than one subject. There were no events that were considered serious, and none that led to withdrawal of treatment.

TEAEs related to status epilepticus and convulsions. TEAEs related to status epilepticus and convulsions occurred in 4 subjects (3.5%) during perampanel exposure (Table 14.3.2.6.8). [REDACTED]

TEAEs related to drug-related hepatic disorder abnormalities: Two subjects had drug-related TEAEs associated with hepatic disorder laboratory abnormalities during perampanel exposure. [REDACTED]

[REDACTED] Neither of these events was serious or resulted in treatment discontinuation, and the subjects recovered from these TEAEs.

Cardiac and ECG TEAEs: Cardiac and ECG-related TEAEs were reported for 7 subjects (6.1%) during perampanel exposure; each of these events was only reported once (Table 14.3.2.6.10). Most of these TEAEs were non-serious and did not result in perampanel discontinuation. [REDACTED]

TEAEs related to rash: TEAEs related to rash occurred in 5 subjects (4.4%) during perampanel exposure (Table 14.3.2.6.11). All of these events were mild or moderate in intensity and none resulted in perampanel discontinuation (Listing 16.2.7.1). Of the 5 subjects who had rash, 4 were taking 8 mg/day and 1 was taking 6 mg/day.

TEAEs related to fall: Reports of fall were systematically queried to exclude reporting of falls that were part of the PGTC seizures. In total, 3 subjects (2.6%) reported 4 TEAEs related to fall during perampanel exposure over a period of 1073.0 subject-months (Table 14.3.2.6.12).

TEAEs related to accident/injury were reported for 21 subjects (18.4%) (Table 14.3.2.6.13). Narratives for subjects who experienced a TEAE of fall are provided in Section 14.3.3.

Other events of interest:

A narrative for this subject is provided in Section 14.3.3.

Narratives for the 30 subjects who had Controlled Substance Staff-identified adverse events are provided in Section 14.3.3.

Analysis of All Adverse Events

At least 1 TEAE occurred in 92 subjects (80.7%) in the Safety Analysis Set during exposure to perampanel in the Core Study and/or Extension Phase. Table 6 presents common TEAEs, ie, those with an incidence of greater than or equal to 5.0%. The incidence of all TEAEs is summarized by MedDRA preferred term (in decreasing order of frequency in the total perampanel group) in Table 14.3.1.3.1 and by MedDRA SOC and preferred term in Table 14.3.1.3.2. Additional summaries are provided of TEAEs by relationship to study treatment in Table 14.3.1.5.2, by MedDRA SOC and preferred term for all treatment-related TEAEs in Table 14.3.1.5.1; by MedDRA SOC, preferred term, and maximum severity in Table 14.3.1.4.1; and by MedDRA SOC, preferred term, and actual perampanel dose at onset in Table 14.3.1.3.3. A summary of non-serious TEAEs is presented in Table 14.3.1.9.1.

Subgroup analyses of TEAEs by MedDRA SOC and preferred term are provided by age in Table 14.3.1.8.1 (Age Group 1) and Table 14.3.1.8.2 (Age Group 2), by sex in Table 14.3.1.8.3, by race in Table 14.3.1.8.4, and by number of AEDs at Core Study baseline in Table 14.3.1.8.5.

Table 6 Treatment-Emergent Adverse Event: Most Common (≥5% in Total Safety Population) - Extension Phase: Safety Analysis Set

MedDRA Preferred Term ^a	Modal Daily Perampanel Dose				Total (N=114) n (%)
	<4 mg/day (N=4) n (%)	4 mg/day (N=7) n (%)	>4 to 8 mg/day (N=84) n (%)	>8 to 12 mg/day (N=19) n (%)	
Subjects With Any TEAE	3 (75.0)	7 (100.0)	66 (78.6)	16 (84.2)	92 (80.7)
Dizziness	0	4 (57.1)	23 (27.4)	8 (42.1)	35 (30.7)
Irritability	0	1 (14.3)	11 (13.1)	2 (10.5)	14 (12.3)
Nasopharyngitis	0	1 (14.3)	8 (9.5)	4 (21.1)	13 (11.4)
Upper Respiratory Tract Infection	1 (25.0)	2 (28.6)	7 (8.3)	3 (15.8)	13 (11.4)
Somnolence	0	4 (57.1)	8 (9.5)	1 (5.3)	13 (11.4)
Fatigue	0	2 (28.6)	8 (9.5)	2 (10.5)	12 (10.5)
Weight Increased	0	0	7 (8.3)	4 (21.1)	11 (9.6)
Headache	0	0	6 (7.1)	3 (15.8)	9 (7.9)
Vertigo	0	1 (14.3)	8 (9.5)	0	9 (7.9)
Insomnia	0	0	6 (7.1)	2 (10.5)	8 (7.0)
Contusion	0	1 (14.3)	6 (7.1)	1 (5.3)	8 (7.0)
Anxiety	0	0	4 (4.8)	2 (10.5)	6 (5.3)

Percentages are based on the total number of subjects in the relevant treatment group.

Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the Core Study, the perampanel exposure consisted of the Core Study plus the Extension Phase treatment duration. For subjects who received placebo in the Core Study, the perampanel exposure consisted of the Extension Phase treatment duration.

A subject with two or more adverse events in the same PT is counted only once for that PT.

MedDRA Version 16.1.

a: Preferred terms are sorted by descending total frequency.

MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects, n = number of subjects with event, PT = preferred term, TEAE = Treatment-Emergent Adverse Event: an adverse event is treatment-emergent if the adverse event started on or after the Date of First Perampanel Dose and before or on the day of (Date of Last Dose +30 days) during the Extension Phase.

Source: [Table 14.3.1.3.1](#).

Laboratory ResultsLaboratory Parameters Over Time

There were no clinically important mean changes in hematology or clinical chemistry laboratory values during exposure to perampanel in the Core Study and/or Extension Phase for the Safety Analysis Set (Table 14.3.4.1.1.1 and Table 14.3.4.2.1.1). Similarly, shift analysis revealed no shifts of clinical concern for hematology or clinical chemistry parameters (Table 14.3.4.1.2.1, Table 14.3.4.1.2.2, Table 14.3.4.1.2.3, Table 14.3.4.2.2.1, Table 14.3.4.2.2.2, and Table 14.3.4.2.2.3).

Markedly Abnormal Laboratory Values

The incidence of markedly abnormal hematology and clinical chemistry laboratory values during exposure to perampanel in the Core Study and/or Extension Phase is summarized by modal perampanel dose in Table 14.3.4.4.1.1 and Table 14.3.4.4.1.3, respectively, and by actual perampanel dose in Table 14.3.4.4.1.2 and Table 14.3.4.4.1.4, respectively. The most common markedly abnormal hematology value was low neutrophils (n=3, 2.7%), while the most common markedly abnormal clinical chemistry values were low bicarbonate (n=4, 3.6%), high potassium (n=3, 2.7%), and high sodium (n=3, 2.7%). A markedly abnormal laboratory value was defined as a laboratory result that worsened in severity to meet modified National Cancer Institute (NCI) toxicity criteria of Grade 2 or higher on treatment (Grade 3 or higher for phosphate).

The number and percentage of subjects with laboratory increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] greater than 3x upper limit of normal [ULN] at any time during the entire perampanel treatment duration was less than 1%. One subject had an increase in ALT of greater than 3x the ULN but less than or equal to 5x ULN. No subject met the criteria for Hy's Law (AST or ALT greater than 3x ULN, total bilirubin greater than 2x ULN, and alkaline phosphatase less than 2x ULN at the same visit and no subject met the criteria for Hy's Law at any time during treatment), and no subject had an increase in any laboratory result of interest greater than 5x ULN at any time during perampanel exposure (Table 14.3.4.4.1.5).

None of the other cases revealed any concerns or trends for a specific laboratory value. Listings of laboratory values for subjects with treatment-emergent markedly abnormal values are provided in Table 14.3.4.4.2.1 [hematology] and Table 14.3.4.4.2.2 [clinical chemistry]). The number of subjects with 2 consecutive abnormal laboratory values during perampanel exposure as a function of baseline laboratory category (low, normal, high) is summarized in Table 14.3.4.4.3.1 (hematology) and Table 14.3.4.4.3.2 (chemistry). The number and percentage of abnormal laboratory records during perampanel exposure by baseline laboratory category is summarized in Table 14.3.4.4.4.1 (hematology) and Table 14.3.4.4.4.2 (chemistry).

Narratives for subjects with select markedly abnormal laboratory values are presented in Section 14.3.3; narrative criteria were a change from baseline of greater than or equal to 2 grades at 2 or more consecutive postbaseline visits, or the last on-treatment postbaseline value must have been a change from baseline of greater than or equal to 2 grades. Note that consecutive postbaseline visits were defined as 2 adjacent visits greater than or equal to 7 days apart. The only exception was phosphate, which required a change of greater than or equal to 3 grades.

Vital Signs, Physical Findings, and Other Observations Related to SafetyVital Signs

There were no clinically important mean changes in vital signs during perampanel exposure in the Core Study and Extension Phase for the Safety Analysis Set; mean changes from baseline to the End of Treatment in blood pressure and heart rate were less than or equal to ± 2.2 mmHg or 1.2 beats per minutes (bpm), respectively (Table 14.3.4.5.1.1). In addition, there were no clinically notable systolic or diastolic blood pressure values, and 1 (0.9%) subject had a notably low pulse rate. Across the entire perampanel treatment duration, 27.9% of subjects had a clinically notable increase in body weight and 4.5% had a clinically notable decrease in body weight (Table 14.3.4.5.3.1). The mean change from baseline in body weight at the End of Treatment was 2.0 kg (range: -22.5, 14.1) (Table 14.3.4.5.1.1).

Columbia Suicide Severity Rating Scale

The results of the C-SSRS are summarized in Table 14.3.4.7.1.1 (incidence by modal daily dose during the Perampanel Treatment Duration) and Table 14.3.4.7.1.2 (by presence/absence at Core Study Lifetime Baseline and modal daily dose), where baseline refers to the baseline assessments from the core study for both perampanel and placebo. Among those who completed the questionnaires, 6 subjects (5.3%) reported suicidal

behavior and/or ideation ([Table 14.3.4.7.1.1](#)). Incidence tables summarizing suicidal ideation and behavior C-SSRS scores are provided by Modal Daily Perampanel Dose in [Table 14.3.4.7.1.1](#) through [Table 14.3.4.7.1.3](#). Shifts in suicidal ideation and behavior are provided in [Table 14.3.4.7.1.4](#) and [Table 14.3.4.7.1.5](#). Summary statistics of the change in severity and intensity from Core Study Lifetime Baseline and from 6 months prior to Baseline of the suicidal ideation C-SSRS score are provided in [Table 14.3.4.7.1.6](#) through [Table 14.3.4.7.1.9](#). Similar displays of suicidal behavior and/or ideation C-SSRS scores by Core Study Randomized Treatment are provided in [Table 14.3.4.7.2.1](#) through [Table 14.3.4.7.2.9](#)

Withdrawal Questionnaire

The results of the withdrawal questionnaire are summarized for the Safety Analysis Set in [Table 14.3.4.8.1](#) (shifts from baseline to end of therapy) and [Table 14.3.4.8.2](#) (shift from end of therapy to follow-up). Few subjects completed the follow-up withdrawal questionnaire because the study is ongoing. Among those who completed the questionnaires, most rated each symptom “none” or “mild” at every evaluation.

Conclusions

Adjunctive treatment with perampanel daily doses up to 12 mg maintained the seizure control established in the Core Study among subjects 12 years and older with inadequately-controlled PGTC seizures. By the end of the blinded Conversion Period of the Extension Phase, subjects who had received prior DB treatment with placebo showed similar efficacy as subjects who received previous DB treatment with perampanel. Relative to data from the Core Study, perampanel administration to this population was similarly safe and well-tolerated, and the safety profile was consistent with that reported for double-blind placebo-controlled studies in partial seizures. In conclusion, perampanel, given as adjunctive therapy, demonstrates a favorable risk/benefit ratio in an adolescent and adult population with inadequately-controlled PGTC seizures.

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