CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202834
Priority or Standard	Standard
Submit Date(s)	December 22, 2011
Received Date(s)	December 22, 2011
PDUFA Goal Date	October 22, 2012
Division / Office	DNP/OND1
Reviewer Name(s)	Martin S. Rusinowitz, MD
Review Completion Date	August 20, 2012
Established Name	Perampanel
(Proposed) Trade Name	Fycompa
Therapeutic Class	Anticonvulsant
Applicant	Eisai, Inc.
Formulation(s)	Immediate release, film coated tablets
Dosing Regimen	Once daily
Indication(s)	Adjunctive treatment of partial onset seizures
Intended Population(s)	12 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Perampanel is safe and effective at doses of 4mg to 8mg daily. It is recommended for approval on the basis of this medical review.

1.2 Risk Benefit Assessment

Efficacy is established based on three adequate and well controlled Phase 3 studies. The evidence for efficacy for perampanel in all three Phase 3 studies was based on reduction in seizure frequency, specifically, the percent change in seizure frequency from baseline of all partial-onset seizures per 28 days, during the double-blind phase in the ITT double-blind population. Study 304 establishes that perampanel is superior to placebo at doses of 8mg and 12mg, Study 305 demonstrates superiority at doses of 8mg and 12mg and Study 306 shows superiority at doses of 4mg and 8mg, but not 2mg.

Safety will be reviewed separately by Dr. Mary Doi. No serious, life threatening, risks have been reported for perampanel. There have been no serious skin reactions, aplastic anemia or Hy's Law cases reported. There appears to be a signal for anger and aggression, particularly in adolescents. Other potential safety signals, including fractures, cholelithiasis, weight gain, and mildly elevated liver enzymes are being further evaluated. Most of these adverse events appear to be more prevalent in the highest dose evaluated (12mg).

The potential benefit of an additional effective anticonvulsant medication clearly outweighs the adverse event profile of perampanel.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

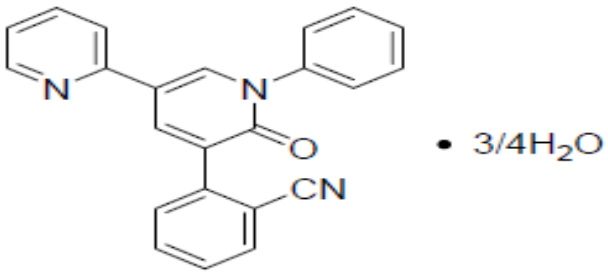
None

2 Introduction and Regulatory Background

2.1 Product Information

Perampanel, a new molecular entity, is an orally active, noncompetitive and highly selective α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists might potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially anti-epileptogenic effects. Perampanel has shown anticonvulsant activity in seizure models in rodents. In a rat model of partial seizures, oral perampanel elevated the "after discharge threshold" at a dose of 10 mg/kg, and reduced seizure severity at 5 mg/kg and 10 mg/kg, while a significant effect on "after discharge duration" was observed at 10 mg/kg. The results in these animal models suggest that perampanel might be effective in the treatment of partial-onset seizures, with or without secondary generalization.

2.1.1 Molecular Formula



Molecular Formula, $C_{23}H_{15}N_3O \bullet 3/4H_2O$

Chemical name: 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3yl)benzonitrile hydrate (4:3) (IUPA)

International Non-proprietary Name (INN): Perampanel

The proprietary name for perampanel is Fycompa ™. Its proposed indication is for the treatment of partial-onset seizures in patients with epilepsy aged 12 years and older.

Perampanel film-coated tablets used in the clinical trials contained 2-, 4-, 6-, 8-, 10-, and 12-mg of perampanel and were round, biconvex, and engraved. In these clinical trials, treatment with perampanel was initiated with a dose of 2 mg/day. This was increased based on clinical response and tolerability by 2 mg/day increments to a dose of 4 mg to 12 mg/day. There was an interval of at least one week between increasing the dose. The maximum dose of perampanel was 12 mg/day. Because of the side-effect of somnolence, dosing is recommended at bedtime, with or without food.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Anticonvulsants in common clinical use for the treatment of partial epilepsy

Phenobarbital
Primidone
Phenytoin
Carbamazepine
Valproic Acid
Gabapentin
Lamotrigine
Topiramate
Tiagabine
Levetiracetam
Oxcarbazepine
Pregablin
Lacosamide
Ezogabine

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety (perampanel) is an NCE (new chemical entity) and not currently marketed.

2.4 Important Safety Issues with Consideration to Related Drugs

Perampanel has a relatively low systemic clearance, in part due to its relatively high plasma protein binding. The average $t_{1/2}$ is 105 hours. Perampanel is primarily eliminated by oxidative metabolism followed by glucuronidation with relatively rapid fecal and urinary excretion of perampanel metabolites. There are no active metabolites.

Clearance of perampanel was significantly increased in the presence of the co-administered CYP3A4 inducers carbamazepine, oxcarbazepine and phenytoin, resulting in lower exposure of perampanel. Phenobarbital and primidone, showed no significant effect on perampanel clearance. In addition, the co-administered AEDs clobazam, clonazepam, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide also had no clinically relevant effect on perampanel clearance or the resulting serum concentration. In a population PK analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day, perampanel did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel had a significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the magnitude of these effects was less than 10% for each drug at the highest perampanel dose evaluated (12 mg/day). Perampanel co-administration resulted in a 26% decrease in oxcarbazepine clearance.

For more detailed discussion refer to section 6.1.7.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Formal discussions regarding the development program and New Drug Application submission for perampanel were held with the FDA on December 5, 2007 at the End of Phase 2 meeting. The issues agreed upon at that meeting included the following:

· The design, duration, study population and endpoints for the Phase 3 studies were acceptable to support the proposed indication for perampanel.

· Phase 3 Study 306, together with the Phase 2 studies 206 and 208, were sufficient to establish the minimal effective dose of perampanel, provided that Study 306 was sufficiently powered.

· Registration of the 8 mg daily dose of perampanel as an effective dose was acceptable provided that efficacy was demonstrated for this dose in at least two of the three Phase 3 studies, and the tolerability profile for this dose was established in relation to lower and higher perampanel doses.

· The primary efficacy endpoint would be the percent change in seizure frequency per 28 days in the Double-blind Phase (Titration Period + Maintenance Period).

· The Intent-to-treat (ITT) Analysis Set would exclude subjects with less than 2 weeks of post-baseline seizure data.

The sponsor subsequently sent the protocols and Statistical Analysis Plan (SAP) to the FDA with a revised primary analysis for the controlled Phase 3 studies. The sponsor proposed the same primary endpoint (percent change in seizure frequency) and ITT analysis set (subjects with at least 2 weeks of post-baseline seizure data) as discussed at the End of Phase 2 meeting, but the analysis proposed would use data collected over the defined Maintenance Period (using a last observation carried forward [LOCF] approach for missing data) instead of the entire Double-blind Phase. This analysis also excluded data during the Titration Period for subjects who completed at least 8 weeks of the Maintenance Period.

On September 13, 2010, in response to the submitted SAP for the controlled Phase 3 studies, DNP reiterated that the ITT population used for primary efficacy analysis should include all subjects who were randomized, took at least one dose of study medication, and had at least one baseline and post-baseline assessment (the Full ITT approach). Based on this, a protocol amendment to Study 305 was made prior to study completion to redefine the primary efficacy analysis. The other Phase 3 Studies 304 and 306 had already been completed before the amendment was made to Study 305. The changes implemented by the protocol amendment to Study 305 were incorporated into the final analyses for Studies 306 and 304 as well.

2.6 Other Relevant Background Information

On July 21, 2011, a Refuse to File letter was sent to Eisai indicating their application was not sufficiently complete to permit a substantive review. In particular, there were inadequate pharmacology/toxicology data regarding fetal observations in pivotal embryo-fetal development studies as well as numerous unsigned and undated pathology reports along with missing pages in the oral toxicity study in rats.

Additionally, there were many inadequacies with regard to clinical safety. Many datasets for the studies performed for non-epilepsy indications were not submitted and the format and organization of the submission did not provide comprehensive hyperlinks. A number of narratives for some serious adverse events (AEs) and dropouts due to AEs were missing. There were inadequacies in the analysis and presentation of the integrated safety data along with problems in the data presented for the analyses of demographic characteristics. There were also a number of impediments to filing with regard to chemistry, manufacturing and controls as well as biopharmaceutics and controlled substance data.

On September 26, 2011, a meeting was held with DNP to discuss the Refuse to File correspondence. Based on the discussion points at this meeting, Esiai submitted a resubmission of their NDA on December 22, 2011. After completing a filing review of this NDA resubmission, DNP communicated with Esiai indicating that their application was sufficiently complete to permit a substantive review.

In accordance with 21 CFR 314.101(a), the application was considered filed 60 days after the date it was received. The review classification for this application was Standard and the user fee goal date is October 22, 2012.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, eCTD format was followed and fully functional. There were numerous errors and inconsistencies with regard to the coding of adverse events and safety reporting. These will be detailed separately by Dr. Mary Doi in her safety review.

3.2 Compliance with Good Clinical Practices

A DSI consultation was submitted on March 27, 2012 requesting clinical inspections of four sites, two for Study 304 and two for Study 305.

Study 304: In this study the treatment effect was significant in US sites but not in Central and South America. Site # 5128, in Jacksonville, Florida was selected because of its large sample size, a high number of protocol violations and a large treatment effect. Site # 1701, in Santiago, Chile was chosen because of a large sample size and a high number of adverse events.

Study 305: Site # 4501, in Goteorg, Sweden was selected because of its large sample size and large treatment effect. Site # 1303, in Leuven, Belgium, was chosen because of a large sample size, large treatment effect and high number of discontinuations.

DSI Inspection Results are pending.

3.3 Financial Disclosures

The Director of Finance and Accounting at Esiai, Michael R. Melfi, has certified that there have been no financial arrangements with the listed clinical investigators whereby the value of compensation to the investigators listed could be affected by the outcome of the study as defined in 21 CFR 54.2(a). He has also certified that each listed clinical investigator has been required to disclose to the sponsor whether the investigator has a propriety interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and none were disclosed. There was further certification that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The complete review is not submitted at the time of this writing, but Dr. Lyndmila Soldatova, from CMC, continues to evaluate the possibility of (b) (4) contamination. She is also evaluating solubility data from perampanel physician sample blister packs.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

The complete review is not submitted at the time of this writing, but Dr. Christopher Toscano has found prolonged covalent binding of either the parent compound, or a metabolite, after 2 years in the aorta and 45 weeks in the eye in animal studies. Although this is of unknown relevance, this may bear some relationship to the safety finding of increased bone fractures.

Although there were animal findings of ataxia and sedation, most of these appeared to reverse over time. Genotoxicology and carcinogenicity studies are apparently negative while there is some evidence of phototoxicity.

There may be some evidence increased seizure activity at higher dosages, perhaps an induction effect.

4.4 Clinical Pharmacology

The complete review is not submitted at the time of this writing, but Drs. Xinning Yang and Joo-Yeon Lee are evaluating the many unidentified metabolites found in clinical pharmacology studies. They are also looking in to changes needed in the starting and maximum dosages in patients with hepatic impairment. There is evidence to suggest that 6mg of perampanel may be the maximum safe dose in such patients.

4.4.1 Mechanism of Action

See section 4.4

4.4.2 Pharmacodynamics

See section 4.4

4.4.3 Pharmacokinetics

See section 4.4

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 9

The following tables of all studies/clinical trials are provided by the sponsor.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	E2007-E044-017	5.3.1.1.1	• To evaluate the absolute oral bioavailability of perampanel following concomitant administration of an intravenous (IV) microdose of ^{14}C-perampanel solution and a single oral dose of perampanel. • To investigate the metabolite profile of perampanel in plasma, urine, and feces and characterize metabolites where appropriate.	Open-label	• Oral: 4 mg tablets, 8 mg dose • IV: perampanel 10 µg labeled with approx. 200nCi of radioactivity (^{14}C) in a solution of not more than 10mL	N=10	Healthy subjects	Single dose	Complete; Final CSR
BA	E2007-E044-003	5.3.1.1.2	To evaluate the pharmacokinetics and pharmacological effects of single oral doses of E2007 in the fed, as compared to the fasted state, in healthy adult male and female volunteers.	Open-label	E2007: 1 mg tablet, oral	N =24	Healthy subjects	Single dose	Complete; Final CSR
BE	E2007-A001-008	5.3.1.2.1	To evaluate the bioequivalence of a new formulation of E2007 (test formulation) compared to a reference formulation, after a single oral dose in healthy subjects.	Open-label	E2007: 2 mg tablets, oral	N=34	Healthy subjects	Single dose	Complete; Final CSR
BE	E2007-E044-016	5.3.1.2.2	To demonstrate dose strength equivalence between two 2 mg E2007 tablets and a single 4 mg tablet.	Open-label	E2007: 2 mg and 4 mg tablets, oral	N=24	Health subjects	Single dose	Complete; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	E2007-E044-037	5.3.1.2.3	To demonstrate bioequivalence between 6 x 2-mg tablets of perampanel and a single 12-mg tablet of perampanel.	Open-label	Perampanel: 2 mg and 12 mg tablets, oral	N=28	Healthy subjects	Single Dose	Complete; Final CSR
BE	E2007-A001-040	5.3.1.2.4	To demonstrate bioequivalence between 6 x 2-mg tablets of perampanel and a single 12-mg tablet of perampanel.	Open-label	Perampanel: 2 mg and 12 mg tablets, oral	N=54	Healthy subjects	Single Dose	Complete; Final CSR
BE	E2007-A001-039	5.3.1.2.5	To demonstrate bioequivalence between 3 x 2-mg tablets of perampanel and a single 6-mg tablet of perampanel	Open-label	Perampanel: 2 mg and 6 mg tablets, oral	N=54	Healthy subjects	Single Dose	Complete; Final CSR
Method Val	EIS-R791R2	5.3.1.4.1	Validation Report for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R791A1	5.3.1.4.2	Validation Report Addendum 1 for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R791R1A2	5.3.1.4.3	Validation Report Addendum 2 for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R1458	5.3.1.4.4	Interference Evaluation of 19 AEDs on E2007 with Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	BTM-1076-R0	5.3.1.4.5	Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	SH09-E01-TR352	5.3.1.4.6	Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	SH09-E01-TR352A1	5.3.1.4.7	Addendum 1 for Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Val	SH09-E01-TR352A2	5.3.1.4.8	Addendum 2 for Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	SHAM-1076-R0	5.3.1.4.9	Determination of E2007 in Human Plasma (Sodium Heparin) by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	GB04062V	5.3.1.4.10	Method Validation for the Determination of E2007 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	GB09008V	5.3.1.4.11	Additional Validation of a Bioanalytical Method for the Determination of E2007 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	105-001	5.3.1.4.12	Validation Report for the Determination of E2007 in Human Plasma by HPLC with Fluorescence Detection	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	891-001b	5.3.1.4.13	Bioanalytical Report for the Comparison of a Validated E2007 HPLC-FLD Method to a Validated E2007 LC-MS/MS Method	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0714-001	5.3.1.4.14	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0714/001, E2007-E044-005)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0751-002	5.3.1.4.15	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0751/002, E2007-E044-006)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	ME0743-002	5.3.1.4.16	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0743/002, E2007-E049-202)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0743-003	5.3.1.4.17	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME047/003, E2007-E049-203)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	105-001v3	5.3.1.4.18	Method Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	238-001	5.3.1.4.19	Validation Report for the Determination of E2007 in Human Plasma by LC-MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	0003-036b	5.3.1.4.20	Sample Analysis Report for the Determination of E2007 in Human Plasma by LC-MS/MS (0003/036b, E2007-E044-025)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v1	5.3.1.4.21	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 1)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v2	5.3.1.4.22	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 2)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	238v3	5.3.1.4.23	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 3)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v5	5.3.1.4.24	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 5)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v6	5.3.1.4.25	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 6)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v7	5.3.1.4.26	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 7)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	228-001	5.3.1.4.27	Validation Report for the Determination of Unbound E2007 in Human Plasma by LC-MS/MS (228/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	228-001v1	5.3.1.4.28	Method Report for the Determination of Unbound E2007 in Human Plasma by LC-MS/MS (228/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	100-001	5.3.1.4.29	Validation Report for the Determination of E2007 in Human Urine by LC-MS/MS (101/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Val	101-001MU	5.3.1.4.30	Partial Validation Method for the Determination of E2007 in Human Urine by LC-MS/MS (101/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401	5.3.1.4.31	Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401A1	5.3.1.4.32	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401A2	5.3.1.4.33	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 2	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603	5.3.1.4.34	Partial Validation Report: Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603Ad1	5.3.1.4.35	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603Ad2	5.3.1.4.36	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 2	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603Am1	5.3.1.4.37	Determination of E2007 in Human Plasma by LC/MS/MS Amendment 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20010551	5.3.1.4.38	Assay Validation for the Quantitative Analysis of Unchanged Drug (E2007) in Human Plasma (E2007-Va02-P)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Val	W-20020096	5.3.1.4.39	Assay Validation for the Quantitative Analysis of Unchanged Drug (E2007) in Human Plasma – The stability of E2007 in frozen human plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20010818	5.3.1.4.40	The Stability of Standard Solutions of the Unchanged Drug (E2007) and the Internal Standard (b) (4) (b) (4)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20011197	5.3.1.4.41	Assay Validation of the Quantitative Analysis of Unchanged Drug (E2007) in Human Urine (E2007-Va03-U)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	QBR101589-2	5.3.1.4.42	Validation of an LC-MS/MS Method for the Measurement of Free and Total E2007 and Metabolites M1, M2, M3, M4, M5 and M7 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	QBR104264-3	5.3.1.4.43	Determination of ethinylestradiol, levonorgesterl and perampanel (E2007) in Human Plasma Samples by LC-MS/MS from Clinical Study E2007-E044-029	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	24-010	5.3.1.4.44	Analysis of Biological Samples Derived from Humans Administered a Single Intravenous Dose of 10 µg/200 nCi C14-Perampanel, for C14-content, by Accelerator Mass Spectrometry (Eisai Study E2007-E044-017)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	B00021	5.3.1.4.45	Quantitative determination of E2007 in rat, dog, human plasma and 1/15 mol/L phosphate buffer (pH 7.4) containing 50 mmol/L NaCL by HPLC with FL detection	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR103785-1	5.3.1.4.46	Determination of E2007 in human plasma samples by LC-MS/MS from clinical study E2007-E044-028	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR105673-1	5.3.1.4.47	Determination of E2007 (Perampanel) in human plasma samples by LC-MS/MS from clinical study E2007-E044-037	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR106309-1	5.3.1.4.48	Determination of E2007 (Perampanel) in human plasma samples by LC-MS/MS from clinical study E2007-E044-030	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	45-0706	5.3.1.4.49	Determination of E2007 in Human Plasma by LC-MS/MS Supporting E2007-A001-023	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Report	45-0707	5.3.1.4.50	Determination of E2007 in Human Plasma by LC-MS/MS Supporting E2007-A001-024	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB05026D	5.3.1.4.51	Determination of E2007 in human plasma from the clinical study entitled Phase I Ascending Single Dose Study of E2007 in Healthy Japanese Male Volunteers (E2007-J081-010)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB07052D	5.3.1.4.52	Determination of E2007 in human plasma from the clinical study entitled Phase I Ascending Repeated-Dose Study of E2007 in Healthy Japanese Male Volunteers (E2007-J081-026)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB09022D	5.3.1.4.53	Determination of E2007 concentration in human plasma from the clinical study entitled "A Phase II, Ascending High-dose, Add-on Study of E2007 in Patients with Refractory Partial Seizures Uncontrolled with other AEDs (E2007-J081-231)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Report	EIS-R1102	5.3.1.4.54	LC/MS/MS Analysis for the Determination of the Concomitant AEDs of E2007 in Human Plasma: A Phase II, Ascending High-dose, Add-on Study of E2007 in Patients with Refractory Partial Seizures Uncontrolled with Other AEDs	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	NB10155E	5.3.1.4.55	Cross validation of the bioanalytical methods for the determination of E2007 in human plasma across various bioanalytical laboratories	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Protein Binding	B00033	5.3.2.1.1	Protein binding of E2007 in rat, dog and human plasma.	Equilibrium dialysis	20 ng/mL 200 ng/mL 2000 ng/mL	N=3 per species	N/A	N/A	Complete; Final Report
Protein Binding	AE-4737-G	5.3.2.1.2	Protein binding of 14C-E2007 to human serum protein in vitro	Equilibrium dialysis	20 ng/mL 200 ng/mL 2000 ng/mL	N=3 per species	N/A	N/A	Complete; Final Report
Hepatic Metabolism	B07001	5.3.2.2.1	Effect of Ketoconazole and CYP3A4 Antibody on the Formation of E2007 Metabolites in Human Liver Microsomes	N/A	1000 ng/mL	N/A	N/A	N/A	Complete; Final Report
Hepatic inhibition	B00030	5.3.2.2.2	Kinetic and Inhibition Studies using Human Liver Microsomes with E2007	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Hepatic inhibition	AE-4739-G	5.3.2.2.3	Inhibitory Study of E2007 for CYP Isoforms Using Human Liver Microsomes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report

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Enzyme induction	GE-0045	5.3.2.2.4	Enzyme Induction Study of E2007 in Primary Cultured Human Hepatocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Metabolites analysis	B05007	5.3.2.2.5	Structural Analysis of E2007 Metabolites Produced by Human Liver Microsomes	N/A	60 µg/mL	N/A	N/A	N/A	Complete; Final Report
Enzyme inhibition	XT095036	5.3.2.2.6	In Vitro Evaluation of E2007 as a Direct Inhibitor of UGT Enzymes in Human Liver Microsomes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Enzyme induction	Xt093050	5.3.2.2.7	In Vitro Evaluation of E2007 as an Inducer of Cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) Expression in Cultured Human Hepatocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Metabolism	B04006	5.3.2.2.8	Estimation of Human CYP Isoforms Response for E2007 Metabolism	N/A	10 ng/mL 30 ng/mL 100 ng/mL	N/A	N/A	N/A	Complete; Final Report
Metabolism	B06012	5.3.2.2.9	Assessment of E2007 Metabolism by Recombinant Human CYP3A5	N/A	10 ng/mL 30 ng/mL 100 ng/mL	N/A	N/A	N/A	Complete; Final Report
Metabolites	B08002	5.3.2.2.10	Comparison of E2007 Metabolites in Rat, Monkey and Human in vitro	N/A	10 µg/mL	N/A	N/A	N/A	Complete; Final Report
Metabolites	B03033	5.3.2.2.11	Comparison of Metabolite Pattern of E2007 after Incubation with Rat, Monkey, Mouse and Human Cryopreserved Hepatocytes	N/A	16.6 µg/mL	N/A	N/A	N/A	Complete; Final Report

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Metabolites	C07139	5.3.2.3.1	Isolation and Identification of E2007 Metabolites in Human Urine	N/A	Human urine samples from E2007-A001-014 6 mg q.d. for 20 days	N/A	N/A	N/A	Complete; Final Report
Metabolic Profile	L07002	5.3.2.3.2	Metabolic Profile of E2007 in Plasma, Urine or Bile after Oral Administration of E2007 to Rat, Monkey and Human	N/A	Rat: 10 mg/kg Monkey: 1 mg/kg Human urine samples from E2007-A001-014 6 mg q.d for 20 days	N/A	N/A	N/A	Complete; Final Report
Cellular Transport	GE-0258-G	5.3.2.3.3	Cellular Transport Study of e2007 Using MDR1 Expressing Cell	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	GE-0404-G	5.3.2.3.4	Transport Study of E2007 using OATP1B1 and OATP1B3 Expressing Oocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	B06015	5.3.2.3.5	Characterization of E2007 Transport via Human Organic Anion and Organic Cation Transporters	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	DMPKT2011-002	5.3.2.3.6	Transport of E2007 across Human Breast Cancer Resistance Protein (BCRP)-Expressed Cell Monolayer and the Inhibition Potency of E2007 on BCRP	N/A	0 to 100 µmol/L	N/A	N/A	N/A	Complete; Final Report
Concentration Ratio	B06013	5.3.2.3.7	Blood to Plasma Concentration Ration of 14C-E2007 in Rat, Dog Monkey and Human	N/A	20 ng/mL 200 ng/mL 2000 ng/mL	N/A	N/A	N/A	Complete; Final Report

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PK	E2007-E044-001	5.3.3.1.1	To evaluate preliminary safety and tolerability of E2007 in healthy male volunteers.	Randomized, double-blind, placebo-controlled	E2007: 0.1 mg, 1mg and 5 mg tablets, doses up to 8 mg, oral	N=55	Healthy subjects	Single dose	Complete; Final CSR
PK	E2007-E044-002	5.3.3.1.2	To evaluate the safety, tolerability, PK and PD of multiple oral doses of E2007 as compared to placebo in healthy adult male subjects.	Randomized, double-blind, placebo-controlled	E2007: 1 mg and 5 mg tablets, doses up to 6 mg, oral	N=32	Healthy subjects	14 Days	Complete; Final CSR
PK	E2007-J081-010	5.3.3.1.3	To evaluate safety, tolerability and PK of a single dose of E2007 when given orally at dose levels of 0.25, 0.5, 1, 2, 4, 6 and 8 mg to healthy Japanese male subjects.	Randomized, double-blind, placebo-controlled	E2007: 0.25 mg, 0.5 mg, 1 mg and 2 mg tablets, doses up to 8 mg, oral	N=56	Healthy Japanese subjects	Single dose	
PK	E2007-E049-203	5.3.3.2.1	• To assess the tolerability and safety of E2007 in patients with refractory partial or generalized seizrures. • To assess the PK of E2007 in epileptic patients receiving at least one concomitant anti-epileptic drug.	Randomized, double-blind, placebo-controlled	E2007: 1 mg and 2 mg tablets, doses up to 2 mg, oral	N=18	Subjects with epilepsy (simple or complex partial or PGTC)	28 Days	Complete; Final CSR
PK	E2007-E044-015	5.3.3.3.1	To determine the effect of impaired hepatic function on the pharmacokinetics of E2007.	Open-label	E2007: 1 mg tablet, 1 mg dose, oral	N=24	Hepatically impaired subjects	Single dose	Complete; Final CSR

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PK	E2007-E044-004	5.3.3.3.2	To evaluate the safety and tolerability of E2007 after single oral administration to generally healthy, elderly, male and female volunteers.	Randomized, double-blind placebo-controlled	E2007: 1 mg tablets, doses up to 2 mg, oral	N=25	Healthy elderly subjects	Single dose	Complete; Final CSR
PK	E2007-E044-007	5.3.3.3.3	To gain information on the absorption, metabolism and elimination of ^{14}C-E2007 after a single-radiolabelled dose in healthy elderly volunteers.	Open-label	E2007: 2 mg tablet, 2 mg dose, oral	N=16	Healthy elderly subjects	Single dose	Complete; Final CSR
PK	E2007-J081-026	5.3.3.3.4	To evaluate the safety, tolerability and PK of E2007 when administered orally at dosages of 2 and 4 mg once daily to Japanese healthy adult male volunteers.	Randomized, placebo-controlled	E2007: 2 mg and 4 mg tablets, doses of 2 mg and 4 mg, oral	N=24	Healthy Japanese subjects	Part 1: 14 days Part 2: 28 days	Complete; Final CSR
PK	E2007-E044-005	5.3.3.4.1	To assess the effect of repeated oral doses of ketoconazole on the PK of single oral doses of E2007 in healthy men.	Randomized, open-label crossover	E2007: 1 mg tablet, dose of 1 mg, oral Ketoconazole: 400mg tablet, 400mg dose, oral	N=26	Healthy subjects	E2007: single dose Ketoconozole :10 Days	Complete; Final CSR
PK	E2007-E044-006	5.3.3.4.2	To compare the pharmacokinetics of a single dose of E2007 before and during treatment with carbamazepine.	Open-label	E2007: 1 mg tablet, 2 mg dose, oral CBZ: 100mg and 200mg tablets, doses up to 300 mg, oral	N=20	Healthy subjects	E2007: two single doses CBZ: 31 days	Complete; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	E2007-A001-014	5.3.3.4.3	To determine the effect of E2007 on the pharmacokinetics of the CYP3A4/5 substrate midazolam.	Open-label	E2007: 2mg tablet, doses up to 6 mg, oral Midazolam: Syrup, 4mg dose (2mL of 2mg syrup), oral	N=35	Healthy subjects	Period 1: midazolam single dose Period 2: E2007 20 days Period 3: E2007 and midazolam single dose	Complete; Final CSR
PK	E2007-E044-019	5.3.3.4.4	To determine the effect of E2007 on the pharmacokinetics of components of the combined ethinylestradiol and levonorgestrel oral contraceptive (OC) pill.	Open-label	E2007: 2 mg tablet, doses up to 4 mg, oral OC: Microgynon® 30 ED memopack/ blister pack 21 active 7 placebo, oral	N=24	Healthy subjects	Period 1: OC 21 days Period 2: OC and E2007 2mg 7 days Period 3: OC and E2007 4mg 21 days	Complete; Final CSR
PK	E2007-E044-025	5.3.3.4.5	To determine the effect of steady-state E2007 on the pharmacokinetics of current Parkinson's disease therapy levodopa in healthy volunteers.	Open-label	E2007: 4 mg tablet, 4mg dose, oral Sinemet®: 110 tablets (containing 10.8mg carbidopa, 100 mg levidopa), oral	N=60	Healthy subjects	Period 1: levodopa single dose Period 2: E2007 alone 19 days Period 3: levodopa singled dose with E2007 steady state	Complete; Final CSR

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PK	E2007-E044-029	5.3.3.4.6	Part A: To investigate the effect of steady state perampanel on the pharmacokinetics (PK) of a single-dose oral contraceptive (OC) containing ethinylestradiol (EE) and levonorgestrel (LN) (Microgynon® 30) Part B: To investigate the effect of repeated dosing of an OC containing EE and LN (Microgynon® 30) on the PK of a single dose of perampanel.	Open-label	E2007: 2 mg tablets, doses up to 12 mg, oral Microgynon® 30: (30µg EE and 150 µg LN), oral	Part A: N=28 Part B: N=24	Healthy subjects	Part A: 72 days Part B: 61 days	Complete; Final CSR
PK	E2007-E044-030	5.3.3.4.7	Part A: To determine the effects upon psychomotor function of a single dose of perampanel when administered alone and in combination with a single dose of alcohol Part B: • To determine the psychomotor function and the cognitive effects of steady-state perampanel when administered alone and in combination with a single dose of alcohol. • To determine the effect on driving performance of a single dose of	Part A: Open-label Part B: randomized , placebo-controlled	Perampanel: 2 mg tablet, doses up to 12 mg, oral; Alcohol: (Smirnoff 40% Black Label Vodka) to 80-100mg/100mL BAL given with equal volume carbonated, caffeine-free and sugar-free beverage, oral	Part A: N=35 Part B: N=24	Healthy subjects	Part A: 51 days Part B: 83 days	Complete; Final CSR

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			perampanel when administered alone and at steady-state, and in combination with a single dose of alcohol.						
Pooled Pop PK	CPMS-E2007-2011-002	5.3.3.5.1	• To characterize the PK profile of perampanel in subjects from Phase 1 studies • Investigate dependence of perampanel PK on dose and time • Identify covariates that explain between subject variability • Quantify magnitude of unexplained variability	N/A	N/A	N=606	N/A	N/A	Complete; Final Report
Pooled Pop PK and PKPD	EMFFR2008/06/00	5.3.3.5.2	To describe the pharmacokinetics of perampanel, the exposure-response relationship between the exposure of perampanel and efficacy in adult patients with epilepsy, and to describe the relationship between perampanel exposure and selected adverse events.	N/A	N/A	206: 143 for PK; 141 for PKPD; 148 for PKPD QT; 143 for PKPD AE. 208: 33 for PK; 42 for PKPD; 42 for PKPD QT; 43 for PKPD AE	N/A	N/A	Complete; Final Report

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Pooled Pop PK and PKPD	CPMS-E2007-2011-003	5.3.3.5.3	To describe the PK of perampanel as adjunctive therapy in subjects with refractory partial seizures and to describe the exposure-response relationship between the exposure of perampanel, efficacy, selected adverse events, withdrawal questionnaires and to assess potential interactions with concomitant AEDs.	N/A	N/A	N=770 for PK N=1109 for PKPD	N/A	N/A	Complete; Final Report
Pooled Pop PK and PKPD	CPMS-E2007-2011-004	5.3.3.5.4	To describe the PK of perampanel as adjunctive therapy in adolescent subjects with refractory partial seizures and to describe the exposure-response relationship between the exposure of perampanel, efficacy, selected adverse events, withdrawal questionnaires and to assess potential interactions with concomitant AEDs.	N/A	N/A	N=74 for PK N=105 for PKPD	N/A	N/A	Complete; Final Report

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PD	E2007-E044-009	5.3.4.1.1	To identify an E2007 dosing regimen suitable to achieve supratherapeutic plasma concentrations in healthy young volunteers.	Part 1: randomized, active- and placebo-controlled Part 2: randomized, double-blind, placebo-controlled	E2007: 2 mg tablets, doses up to 10 mg, oral Diazepam: 5 mg tablets, 5 mg dose, oral	Part 1: N=32 Part 2: N=20	Healthy Subjects	Part 1: single dose Part 2: 21 days	Complete; Final CSR
PD	E2007-A001-013	5.3.4.1.2	To quantify the effect of perampanel on the QT interval duration in healthy subjects.	Double-blind, active- and placebo-controlled	Perampanel: 2 mg tablets, doses up to 12 mg, oral Moxifloxacin: 400 mg over-encapsulated, oral	N=261	Healthy Subjects	16 Days	Complete; Final CSR
PD	E2007-E044-020	5.3.4.1.3	To investigate the potential of perampanel to induce skin phototoxicity to ultraviolet and visible light in healthy volunteers.	Randomized, placebo- and active-controlled	Perampanel: 2 mg tablets, doses up to 6 mg, oral Ciprofloxacin: 500 mg tablet	N=36	Healthy subjects	Perampanel: 10 days Ciprofloxacin 10 days	Complete; Final CSR
PD	E2007-A001-023	5.3.4.1.4	To determine the safety and tolerability of single oral escalating doses of perampanel for the purposes of identifying the maximum tolerated dose (MTD) in healthy adult, recreational polydrug users.	Randomized, Double-blind, placebo-controlled	Perampanel 2 mg tablets, 8mg, 12mg, 16mg, 20mg, 24 mg, 28 mg, 32mg, 36mg doses, oral	N=56	Healthy recreational drug users	Single dose	Complete; Final CSR

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PD	E2007-A001-024	5.3.4.1.5	To evaluate the abuse potential of single doses of perampanel compared to alprazolam, oral ketamine, and placebo in healthy recreational polydrug users.	Randomized, double-blind, placebo- and active-controlled	Perampanel: 2 mg tablets, doses of 8 mg, 24 mg and 36 mg, oral Alprazolam: 0.5 mg and 1.0 mg overencapsulated tablets, oral Ketamine: 100 mg solution, oral	N=40	Healthy recreational drug users	Single dose	Complete; Final CSR
Phase 2 Safety Efficacy	E2007-A001-206	5.3.4.2.1	To determine the maximal tolerated dose (MTD) of E2007 given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures)	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg, 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=153	Subjects with refractory partial-onset seizures	14 weeks	Complete; Final CSR
Phase 2 Safety Efficacy	E2007-G000-208	5.3.4.2.2	To determine the safety and tolerability of doses up to a maximum of 12 mg per day of E2007 (perampanel) in patients with refractory partial seizures who were taking inducing and noninducing anti-epileptic drugs (AEDs).	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=48	Subjects with refractory partial-onset seizures	16 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-G000-304	5.3.5.1.1	To evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 8mg and 12 mg, oral	N=390	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR

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Phase 3 Efficacy	E2007-G000-305	5.3.5.1.2	To evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 8 mg and 12 mg, oral	N=389	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-G000-306	5.3.5.1.3	To evaluate the efficacy of three doses of perampanel (2, 4, and 8 mg) given ad adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 2mg, 4mg and 8 mg, oral	N=712	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR
Phase 2 Safety	E2007-E044-205	5.3.5.2.1	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinson's disease (PD) with "wearing-off" motor fluctuations and on-period dyskinesias.	Open-label	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=185	Subjects with idiopathic PD	48 months	Complete; Final Synoptic CSR
Phase 3 Safety	E2007-G000-318	5.3.5.2.2	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinsons' disease (PD) who experienced end-of-dose "wearing-off" motor fluctuations.	Open-label	Perampanel: 2mg tablets, doses up to 4 mg, oral	N=328	Subjects with idiopathic PD	56 weeks	Complete; Final Synoptic CSR
Phase 2 Safety	E2007-A001-220	5.3.3.2.3	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinson's disease (PD) who experienced end-of-dose "wearing-off" motor fluctuations.	Open-label	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=26	Subjects with idiopathic PD	54 weeks	Complete; Final Synoptic CSR

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Phase 2 Safety	E2007-G000-228	5.3.5.2.4	To evaluate long-term (1-year) safety while administering perampanel to patients with PDN or PHN.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=262	Subjects with PDN or PHN	1 year	Complete; Final CSR
Phase 2 Safety	E2007-J081-231	5.3.5.2.5	To explore the safety and tolerability of E2007 up to 12 mg coadministered with other AEDs	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=32	Subjects with refractory partial-onset seizures	10 weeks	Complete; Final CSR
Phase 3 Safety	E2007-G000-303	5.3.5.2.6	To evaluate the long-term safety and tolerability of perampanel as an adjunctive therapy in levodopa treated Parkinson's disease (PD) subjects with motor fluctuation.	Open-label	Perampanel: 2 mg tablets, doses up to 4 mg	N=1005	Subjects with idiopathic PD	108 weeks	Complete; Final Synoptic CSR
ISS	N/A	5.3.5.3.1	Integrated Summary of Safety	N/A	N/A	N/A	N/A	N/A	Final Report
ISE	N/A	5.3.5.3.2	Integrated Summary of Efficacy	N/A	N/A	N/A	N/A	N/A	Final Report
Assessment of Abuse Potential	N/A	5.3.5.3.3	Abuse Potential Evaluation Report	N/A	N/A	N/A	N/A	N/A	Final Report
Phase 2 Safety	E2007-A001-207	5.3.5.4.1	To evaluate the safety and tolerability of perampanel given as adjunctive, long-term treatment in subjects with refractory partial seizures with or without secondary generalization.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=138	Subjects with refractory partial-onset seizures	436 weeks	Ongoing; Interim Synoptic CSR

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Phase 3 Safety	E2007-G000-307	5.3.5.4.2	To evaluate the safety and efficacy of perampanel (up to 12 mg/day) given as adjunctive treatment in subjects with refractory partial seizures.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=1218	Subjects with refractory partial-onset seizures	TBD	Ongoing; Interim Synoptic CSR
BA	E2007-E044-028	5.3.5.4.3	To compare relative bioavailability between a 4 mg dose of an oral suspension of perampanel and a 4 mg tablet of perampanel.	Open-label	Perampanel: 2 mg tablet, dose of 4 mg, oral 0.5 mg/mL suspension, 4 mg dose in 8 mL suspension, oral	N=16	Healthy subjects	Single-dose	Complete; Final Report
Imaging	E2007-A001-226	5.3.5.4.4	To assess the displacement of striatial [^{123}I]-IBZM binding by carbidopa/levodopa in Hoehn and Yahr II-IV Parkinsin's disease (PD) subjects.	Double-blind, placebo-controlled	Perampanel: 2 mg tablet, doses up to 4 mg, oral	N=1	Subjects with idiopathic PD	28 days	Complete; Final Synoptic CSR

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Phase 2 PK and Safety	E2007-E049-202	5.3.5.4.5	To assess the tolerability and safety of E2007 when given to Parkinson's disease patients receiving a stable dose of levodopa and other antiparkinsonian medications.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg tablet, doses up to 2 mg, oral	N=19	Subjects with idiopathic PD	28 days	Complete; Final CSR
Phase 2 Safety and Efficacy	E2007-E044-204	5.3.5.4.6	To compare the efficacy of 3 different doses of E2007 with placebo (in addition to stable antiparkinsonian treatment) on the duration of "off time" during the waking day in Parkinson's disease patients with "wearing-off" motor fluctuations and "on" period dyskinesias	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg tablet, doses up to 2 mg, oral	N=263	Subjects with idiopathic PD	12 weeks	Complete; Final CSR
Phase 2 MTD	E2007-A001-214	5.3.5.4.7	To determine the tolerability of doses up to a maximum of 8 mg per day of perampanel among subjects with Parkinson's disease who experienced end-of-dose "wearing-off" motor fluctuations.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 8 mg, oral	N=75	Subjects with idiopathic PD	10 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-E044-301	5.3.5.4.8	To compare the efficacy of 2 mg perampanel, 4 mg perampanel and placebo on motor function in subjects with Parkinson's disease (PD) who were on optimized and stabilized therapy and experiencing end-of-dose "wearing off" motor fluctuations.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=764	Subjects with idiopathic PD	30 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-A001-302	5.3.5.4.9	To compare the efficacy of 2 mg and 4 mg of perampanel and placebo on duration of daily "OFF" state in subjects with Parkinson's disease (PD) who experienced end-of-dose "wearing off" motor fluctuations.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=752	Subjects with idiopathic PD	20 weeks	Complete; Final Abbreviated CSR
Phase 3 Efficacy	E2007-G000-309	5.3.5.4.10	To compare the efficacy and safety of 1 dose strength (4 mg) of perampanel with that of placebo on motor function in subjects with Parkinson's disease (PD) who were on optimized and stabilized therapy and experienced end-of-dose "wearing off" motor fluctuation.	Randomized, double-blind, placebo- and active-controlled	Perampanel: 2 mg tablets, doses up to 4 mg, oral Entacapone: 200 mg capsules, oral	N=723	Subjects with idiopathic PD	18 weeks	Complete; Final Abbreviated CSR
Phase 2 Safety and Efficacy	E2007-A001-210	5.3.5.4.11	To evaluate the efficacy and safety of E2007 (perampanel) in reducing migraine headaches based on the change in the frequency of migraine periods per 28 days during the treatment phase compared to the baseline phase.	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg and 1.0 mg tablets, doses up to 2 mg, oral	N=206	Subjects with history of migraine	14 weeks	Complete; Final CSR
Phase 2 Safety and Efficacy	E2007-A001-218	5.3.5.4.12	To evaluate perampanel for evidence of efficacy with respect to pain reduction in subjects with PHN.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=146	Subjects with PHN	15 weeks	Complete; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Safety and Efficacy	E2007-G000-227	5.3.5.4.13	To provide evidence of the effectiveness of perampanel for treating the pain associated with PDN.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=355	Subjects with Type I or II diabetes with PDN	15 weeks	Complete; Final CSR
Phase 2 Safety	E2007-E049-201	5.3.5.4.14	To assess the tolerability, safety and PK of E2007 in patients with multiple sclerosis.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg tablets, doses up to 3 mg, oral	N=27	Subjects with multiple sclerosis	28 days	Complete; Final CSR
Phase 2 Safety	E2007-J081-233	5.3.5.4.15	To evaluate the safety and tolerability of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=21	Japanese subjects with refractory partial-onset seizures	112 weeks	Ongoing; Interim CSR

AED=Antiepileptic drug; BA=Bioavailability; BE=Bioequivalence; CSR=Clinical Study Report; E2007=perampanel; IV=Intravenous; MTD=Maximum Tolerated Dose; PK=pharmacokinetic; PD=Pharmacodynamic or Parkinson's disease; PDN=Painful Diabetic Neuropathy; PHN=Post-herpetic Neuralgia; N/A = Not Applicable; Val=Validation

5.2 Review Strategy

The submission was in eCTD format which allowed review of the sponsor's narrative ISE and ISS and analysis using individual study and ISS datasets.

Safety will be reviewed separately by Dr. Mary Doi.

The primary demonstration of efficacy of perampanel therapy in the treatment of partial-onset seizures, with or without secondary generalization, was shown in three multicenter and multinational Phase 3 studies: E2007-G00-304 ("304"), E2007-G000-305 ("305") and E2007-G000-306 ("306"). These were supported by two Phase 2 studies, E2007-A001-206 ("206") and E2007-G000-208 ("208") and an open label extension (OLE) study, E2007-G000-307 ("307").

5.3 Discussion of Individual Studies/Clinical Trials

PHASE 3 STUDY 304

Title of Study: **A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.**

Study Centers: **77 centers in Argentina, Canada, Mexico and the United States.**

Publication: **None**

Studied Period: **April 30, 2008 to November 11, 2010**

Objectives: **The primary objective was to evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.**

Methodology: **This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of three treatment groups (placebo or 8, 12 mg perampanel). The Double-blind Phase included a 6-week Titration Period followed by a 13-week Maintenance Period, during which the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.**

Number of Subjects: **Planned: 375 subjects. Randomized: 390 subjects. Completed: 320 subjects.**

***Diagnosis and Main Criteria for Inclusion*:** **Male and female subjects 12 years of age or older were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.**

Test Product, Dose, and Mode of Administration: **Perampanel was supplied as 2mg tablets and administered orally at bedtime.**

Reference therapy, dose and mode of administration: **The reference therapy was placebo administered orally as matching tablets at bedtime.**

Duration of Treatment: **The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).**

Criteria for Evaluation:

Efficacy: **The primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was percent change in the frequency of complex partial plus secondarily generalized seizures. The primary endpoints, the secondary endpoints, and many of the exploratory endpoints were based on seizure counts from subject diaries. Other exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.**

Safety: **Safety assessments included prior and concomitant medication use, AEs, withdrawals due to AEs, clinical laboratory results, vital signs, ECGs, physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.**

Statistical Methods: **The full ITT analysis set included all randomized subjects who received study drug and had any seizure frequency data from the Double-blind Phase. The ITT analysis set included all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from both the Prerandomization and Double-blind Phases. For the analysis of percent change in seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. Log-transformation based ANCOVA was conducted to assess the robustness of the analysis method. A dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. A closed, sequential testing procedure, was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoint for different dose groups.**

PHASE 3 STUDY 305

Title of the Study: **A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.**

Study Centers**: 84 centers in Australia, Austria, Belgium, Finland, France, Germany, Greece, India, Israel, Italy, Netherlands, Russian Federation, South Africa, Sweden, United Kingdom, and the United States.**

Publication: **None**

Study Period: **May 20, 2008 to January 14, 2011**

Objectives: **The primary objective was to evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.**

Methodology: **This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of three treatment groups (placebo or 8, 12 mg perampanel). The Double-blind Phase included a 6-week Titration Period followed by a 13-week Maintenance Period, during which the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.**

Number of Subjects: **Planned: 375 subjects. Randomized: 389 subjects. Completed: 321 subjects.**

Diagnosis and main criteria for Inclusion: **Male and female subjects 12 years of age or older were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.**

Test Product, Dose, and Mode of Administration: **Perampanel was supplied as 2mg tablets and administered orally at bedtime.**

Reference therapy, dose and mode of administration: **The reference therapy was placebo administered orally as matching tablets at bedtime.**

Duration of Treatment: **The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).**

Criteria for Evaluation:
Efficacy: **The primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was percent change in the frequency of complex partial plus secondarily generalized seizures. The primary endpoints, the secondary endpoints, and many of the exploratory endpoints were based on seizure counts from subject diaries. Other**

exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.

Safety: **Safety assessments included prior and concomitant medication use, adverse events (AEs), withdrawals due to AEs, clinical laboratory results, vital signs, ECGs, physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.**

Statistical Methods: **The Full ITT Analysis Set included all randomized subjects who received study drug and had any seizure frequency data from the Double-blind Phase. The ITT analysis set with at least 14 days of seizure data during treatment included all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from both the Prerandomization and Double-blind Phases. For the analysis of percent change in seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on the rank transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. Log-transformation based ANCOVA was conducted to assess the robustness of the analysis method. A dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoint for different dose groups.**

PHASE 3 STUDY 306

Title of the Study: **A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.**

Study Centers: **116 centers in Asia, Australia, Europe, and Russia.**

Publication: **None**

Study Period: **August 4, 2008 to May 19, 2010**

Objectives: **The primary objective was to evaluate the efficacy of three doses of perampanel (2, 4, and 8 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.**

Methodology: **This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of four treatment groups (placebo or 2, 4, 8 mg perampanel). The Double-blind Phase began with a 6-week Titration Period, during which the subjects had their doses increased to the randomized dose level. During the subsequent 13-week Maintenance Period, the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.**

Number of Subjects: **Planned: 680 subjects. Randomized: 712 subjects. Completed: 623 subjects.**

***Diagnosis and Main Criteria for Inclusion*:** **Male and female subjects 12 years of age or older (18 years of age or older in some countries) were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.**

Test Product, Dose, and Mode of Administration: **Perampanel was supplied as 2mg tablets and administered orally at bedtime.**

Reference therapy, dose and mode of administration: **The reference therapy was placebo administered orally as matching tablets at bedtime.**

Duration of Treatment: **The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).**

Criteria for Evaluation:
Efficacy: **Efficacy assessments included seizure counts from subject diaries, Clinical and Patient Global Impression of Change questionnaires, and the Quality of Life in Epilepsy Questionnaire (QOLIE-31-P). The primary efficacy endpoint was the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase. The responder rate was a secondary efficacy endpoint. Other secondary efficacy endpoints included the percent change in the frequency of complex partial seizures plus secondarily generalized seizures in the Maintenance Period relative to the Prerandomization Phase, and a dose-response analysis of the percent change in seizure frequency.**

Safety: **Safety assessments included prior and concomitant medication use, AEs, withdrawals due to AEs, clinical laboratory results, vital signs, ECGs,**

physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.

Statistical Methods: **The primary efficacy analyses were based on the ITT Analysis Set (all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from the Prerandomization Phase and at least 2 weeks of seizure frequency data from the Double-blind Phase) using LOCF imputation. Sensitivity analyses were based on all randomized subjects with any seizure data during study treatment, on all subjects in the ITT Analysis Set who completed the study, and on the PP Analysis Set, which excluded subjects with major protocol deviations and low compliance. Percent changes in seizure frequencies were analyzed using an ANCOVA with treatment and pooled countries as factors, and seizure frequency in the Prerandomization Phase as a covariate. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. The dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoints.**

PHASE 2 STUDY 206

***Title of Study*: A Double-Blind, Placebo-Controlled, Dose -Escalation, Parallel-Group Study of E2007 Given as Adjunctive Therapy in Patients with Refractory Partial Seizures**

***Studied Period*: March 8, 2005 to February 6, 2007**

***Objectives*: The primary objective of this study was to determine the MTD of perampanel given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures). The secondary objectives were to evaluate the safety, efficacy, concentration-efficacy relationship, and pharmacokinetics of perampanel and its effects on the Profile of Mood States (POMS) test.**

***Methodology*: The trial was a double-blind, placebo-controlled, dose-escalation, parallel-group study with 3 arms: Drug-treated using BID dosing, drug-treated using QD dosing and placebo-treated. Within groups, subjects were stratified 1:1 according to their concomitant AEDs into one of 2 categories: (1) induced (treated with one or a maximum of 2 marketed and approved antiepileptic inducer medications such as carbamazepine, phenytoin, phenobarbital, or primidone) and (2) non-induced (treated with one or a maximum of 2 marketed and approved antiepileptic non-inducer medications such as topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or**

levetiracetam, and none of the drugs in the induced group). To be enrolled, a 4 week retrospective Baseline using the subject's seizure calendar was evaluated. The study consisted of the following phases:

1. Baseline Phase (4 weeks): Prospective ascertainment of seizure frequency based on the subject's seizure calendar.

2. Titration Phase (up to 8 weeks): Subjects were titrated from a starting dose of 1 mg/day (0.5 mg BID or 1 mg QD). The dose was increased every 2 weeks up to 4 mg/day or the MTD. Subjects suffering intolerable AEs were to have the dose reduced one step. Once reduced, the same dose was to be continued until the end of the Maintenance Phase. PK samples were obtained at each visit.

3. Maintenance Phase (4 weeks): The perampanel dose was given at the MTD that each subject maintained during the Titration Phase, and PK samples were obtained at each visit. At the last Maintenance Visit, all completing subjects (including the placebo group) were started on 1 mg/day of the study drug.

4. Transition Phase (2 weeks): Subjects were maintained on 1 mg/day of study drug. After 2 weeks, a final visit was conducted and subjects were withdrawn from study drug treatment. Subjects were to return for the Safety Visit 4 weeks later.

***Number of Patients*: 144 subjects were planned; 153 subjects were analyzed for safety; 152 subjects were analyzed for efficacy.**

***Diagnosis and Main Criteria for Inclusion*: Male and nonpregnant females who had a diagnosis of refractory partial seizures, were treated with 1 or a maximum of 2 other AEDs, and met all other inclusion criteria and none of the exclusion criteria.**

***Test Product, Dose and Mode of Administration*: Perampanel was formulated as 0.5 mg, 1 mg and 2 mg tablets for oral administration.**

***Duration of Treatment*: 14 weeks (8-week Titration, 4-week Maintenance and 2-week Transition Phases)**

***Criteria for Evaluation*: Efficacy was assessed by seizure counts (subject's diary), Clinical Global Impression of Change (CGI), Patient's Global Impression of Change (PGI) and the Seizure Severity Questionnaire.**

***Primary Endpoint*: Determination of the MTD for each subject was a primary study endpoint. For the trial the MTD was defined as the maximum tolerated dose by the majority of the subjects up to a maximum of 4 mg per day.**

***Efficacy*: The proportion of responders during the Maintenance Phase in the ITT Population constituted the primary endpoint analysis**
Safety: Safety was evaluated using frequency and severity of AEs; physical, neurological and ophthalmological (at selected sites) examinations; 12-lead ECG; and laboratory assessments including hematology, clinical chemistry and urinalysis during the trial period.

***Statistical Methods*: Data analysis, tabulations of descriptive statistics and inferential statistics were performed using SAS. The following subject populations were defined for data analyses:**
Safety Population: Subjects included in the safety analysis were those who were randomized and took at least one dose of double-blind study drug.
Intent-To-Treat Population: Subjects included in the ITT analysis were those who both were included in the Safety Population and had at least 2 weeks of Baseline, and had at least one week of Titration and/or Maintenance seizure frequency data.
Per Protocol/Fully Evaluable Population: Subjects included in the Per Protocol/Fully Evaluable analysis were those who were included in the ITT Population, did not have any major protocol deviations/violations and were at least 80% compliant with the study drug at Week 13 as well as during the entire Maintenance Phase.
Efficacy: The primary efficacy variable was the proportion of responders in the ITT-LOCF Population in the Maintenance Phase. A subject was a responder if they experienced a 50% or greater reduction in seizure frequency from the Baseline Phase. Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.

Statistical significance at $\alpha < 0.05$ (2-sided) in the ITT-LOCF Population was required to establish the efficacy of perampanel vs. placebo. Supportive analyses of the ITT-LOCF and FE Populations were conducted for secondary efficacy measures. Other secondary efficacy endpoints included assessments of the proportion of responders at other intervals and for subsets of the ITT Population, the percent change in seizure frequency from baseline, seizure freedom, seizure severity, and subjective assessments of the subjects' improvement during the study (CGIC and PGIC) and of their mood (POMS). Categorical variables (proportion of responders, percent reduction in seizure frequency, percent of subjects who achieve seizure-free status, no significant change in seizure frequency, significant increase in seizures, CGIC, PGIC, and the percentage of subjects needing back titration) were analyzed by using a CMH test stratified by center. Continuous variables (percent change in seizure frequency and the percent change in partial seizure frequency, the number of seizure-free days per 28 days, changes in the Seizure Severity Questionnaire) were analyzed by using ranked ANOVA with terms for treatment and center in the model.

PHASE 2 STUDY 208

***Title of Study*: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Explore the Safety and Tolerability of Doses of perampanel up to a Maximum of 12 mg in Patients with Refractory Partial Seizures.**

***Studied Period*: March 13, 2007 to January 15, 2008**

***Objectives*:**
Primary:
The primary objective of this study was to determine the safety and tolerability of doses up to a maximum of 12 mg per day of perampanel in patients with refractory partial seizures who were taking inducing and noninducing AEDs.
Secondary:
- **Investigate the efficacy of perampanel for the treatment of partial seizures**
- **Explore the relationship between perampanel plasma concentrations and safety and efficacy measurements.**

Exploratory:
- **Determine the proportion of responders at the MTD in the Maintenance Phase.**

***Methodology*: This was a randomized, double-blind, placebo-controlled, parallel-group study. Subjects were initially stratified (inducers vs. non-inducers of the cytochrome P450 3A4 isoenzyme) according to their concomitant AEDs, with the aim to recruit approximately 24 subjects to each stratum. Following stratification, subjects were then randomized to 1 of 2 double-blind treatment groups in a 3:1 ratio (perampanel to placebo) such that, within each stratum, approximately 18 subjects were to receive perampanel and approximately 6 subjects were to receive placebo. All subjects were to receive treatment for a total of 16 weeks (Days 1 to 112). Induced subjects were to be treated with 2 to 3 (maximum) marketed and approved anti-epileptic inducer medications such as: carbamazepine, phenytoin, phenobarbital, or primidone. Non-induced subjects were to be treated with 2 to 3 marketed and approved anti-epileptic noninducer medications such as: topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or levetiracetam, and none of the drugs in the inducer group. Subjects on multiple AEDs were to be considered as induced if at least 1 concomitant medication was an inducer. The study was to consist of the following phases:**
- **Baseline Phase (4 weeks, Days –28 to –1): prospective ascertainment of seizure frequency based on the subject's diary. To be enrolled into the study, a 4-week retrospective baseline using the subject's diary was to be evaluated.**
- **Titration Phase (12 weeks, Days 1 to 84): During the dose-titration period, study drug dosing in the perampanel group was to be started at 2 mg once daily**

and titrated up to 12 mg. Titrations were to be made at 2-week intervals on the basis of individual tolerability and in 2-mg incremental steps. Subjects were to be instructed to take the study drug in the evening with food, except on Visit Days 1, 15, 29, 43, 57, 71, and 85. On only those days, subjects were to receive their study drug with food during their clinic visit. At each titration step, the investigator was to review all data available for each subject. The dose was only to be increased if, in the opinion of the investigator and with the agreement of the subject, the current dose had been adequately tolerated. Subjects who did not tolerate the study drug during the first 2 weeks of treatment were to be withdrawn and not replaced. Subjects who did not tolerate the study drug from the third to the twelfth week of treatment could have remained on the same dose or had their dose reduced to their previously tolerated dose (subjects receiving placebo were to have a sham down-titration). Only 1 dose reduction was to be allowed, and any subject requiring more than 1 dose reduction was to be withdrawn and was not to be replaced. Any subject judged to require dose reduction between visits was to return to the study center for an unscheduled visit. During this phase, a blood sample for plasma concentrations of concomitant AEDs was to be obtained at Visit 2 (Day 1).

- **Maintenance Phase (4 weeks, Days 85 to 112): During the Maintenance Phase, the subject was to continue using the final dose reached during the Titration Phase. No further dose reductions were to be allowed, although the investigator retained the option to withdraw the subject at any time. At the end of the Maintenance Phase (Day 113), blood samples for plasma concentrations of perampanel and other concomitant AEDs were to be obtained for PK analysis. During this phase, blood samples for plasma concentrations of perampanel and concomitant AEDs were to be obtained at Visits 8, 9, or at a Premature Discontinuation Visit (if applicable).**
- **Follow-up Phase (4 weeks, Day 113 to 141): All subjects were to return for end-of-study assessments. Subjects were to return to the study center for monitoring during dose-titration steps (Days 15, 29, 43, 57, 71), at the end of the Titration Phase (Day 85), and at the end of the Maintenance Phase (Day 113). During the dose-titration steps, subjects were to be observed in the study center and discharged at the discretion of the investigator. An observation period of 2 hours after dosing was required. All subjects were to be contacted by telephone on the day following dose administration and again at the midpoint of the 4-week Maintenance Phase to determine if any adverse events had occurred following dosing at the new dose level.**

***Number of Subjects*:**

- **48 subjects were planned**
- **55 subjects were screened and 48 subjects were enrolled and randomized**
- **38 subjects were randomized to the perampanel group and 10 subjects were randomized to the placebo group**

- **48 subjects were analyzed for safety (i.e., all randomized subjects)**
- **47 subjects were analyzed for efficacy (1 subject, subject #1030 in the placebo group, was excluded from the ITT population due to an invalid baseline seizure diary)**

***Diagnosis and Main Criteria for Inclusion*: Eligible subjects were male or female aged 18 to 70 years, inclusive, with the diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according with the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Subjects had to have uncontrolled partial seizures despite having been treated with at least 3 different AEDs (given concurrently or sequentially) for at least 2 years, and they had to have an average of at least 3 partial seizures per month, with no 21-day seizure free period during the 2 months preceding randomization. Simple partial seizures without motor signs were not to be counted towards this inclusion criterion. Subjects were currently being treated with 2 to 3 (maximum) marketed and approved AEDs and were known to take their medications as directed. Use of a vagal nerve stimulator was not to be considered an AED by this criterion. Subjects were to have been on a stable dose of the same AEDs for 1 month prior to Visit 1.**

***Test Product, Dose and Mode of Administration*: perampanel, 2 mg tablets, oral**

***Duration of Treatment*: 16 weeks**

***Criteria for Evaluation*:**
Efficacy: Seizure counts (recorded in a diary); Clinical Global Impression of Change; and Patient Global Impression of Change.
Dose Tolerability and PK: Tolerability of dose (MTD) and AED plasma concentrations.
Safety: Physical and neurological examination; AEs; orthostatic vital signs; ECG; and laboratory assessments.

***Statistical Methods*:**
Analysis populations were the Safety Population, the ITT Population, and the FE Population. The primary efficacy analysis was performed on the ITT Population.
Efficacy:
The primary efficacy endpoint was the proportion of responders in the active treatment group during the Maintenance Phase. A subject was said to have been a responder for a time period if she/he experienced a 50% or greater reduction in seizure frequency per 28 days from the Baseline Phase. Seizure frequency was based on the total number of seizures during that period (as recorded in the subject's diary), rescaled to a 28-day-frequency.

Secondary efficacy endpoints were:

1. Proportion of responders during the Maintenance Phase, Maintenance observed cases (OC), the Titration Phase, each dose phase (2-mg dose phase, 4-mg dose phase, …, 12-mg dose phase), the Overall Treatment Phase (= 12-week Titration Phase plus 4-week Maintenance Phase), 6-week Maintenance (= last 2 weeks of the Titration Phase plus the Maintenance Phase), and the Follow-up Phase.

2. Percentage change in seizure frequency per 28 days from the Baseline Phase to each of the same phases listed in item (1) above.

3. Proportion of subjects experiencing 0 to 25%, > 25% to 50%, > 50% to 75%, > 75% to 100% reduction/increase and > 100% increase in seizure frequency per 28 days from the Baseline Phase to each of the same phases listed in item (1) above.

4. Number of days without seizures per 28 days (during each of the same phases listed in item (1) above.

5. Change from baseline in the Clinician's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.

6. Change from baseline in the Patient's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.

Exploratory efficacy endpoints were:
1. Proportion of responders at the Study MTD.
2. Change from baseline in seizure frequency per 28 days at the Study MTD.
3. Determination of the Response Ratio (RRatio).

Safety:
The primary safety endpoint was the MTD for perampanel. Other safety parameters were AEs, physical and neurological examination findings, laboratory assessments, discontinuations due to study medication, orthostatic vital signs, and ECG findings.

PHASE 3 STUDY 307

***Title of the Study*: An Open-label Extension Phase of the Double-blind, Placebo-controlled, Dose-escalation, Parallel-group Studies to Evaluate the Efficacy and Safety of Perampanel Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures**

***Study Period*: October 17, 2008 to December 1, 2010**

***Objectives*: The primary objective was to evaluate the safety and tolerability of perampanel (up to 12 mg/day) given as adjunctive treatment in subjects with refractory partial seizures. The secondary objective was to evaluate the maintenance of effect of perampanel for the control of refractory partial seizures.**

***Methodology*: This was an OLE study for subjects who completed one of the following DB, placebo-controlled Phase 3 studies: 304,305, or 306. This OLE study consisted of two phases: an Open-label Treatment Phase (comprised of a 16-week blinded ConversionPeriod and a 256-week Maintenance Period) and a Follow-up Phase (4 weeks). During the Conversion Period, subjects and investigators remained blinded to the treatment received in the previous DB study. To achieve this, all subjects continued to take six tablets of study medication (2-mg perampanel or matching placebo) or fewer as they were instructed during the core DB study. An InteractiveVoice Response System (IVRS) was used to provide dosing instructions to the site for each subject enrolled in the OLE study. Subjects who had been assigned to placebo in the core DB study were started on blinded treatment with perampanel 2 mg/day and were titrated to the MTD of perampanel, (up to 12 mg/day). Subjects assigned to a perampanel arm in the core DB study continued to receive perampanel on a blinded basis. The daily dose of perampanel was titrated upwards to 12 mg/day or the MTD for subjects who had achieved a daily perampanel dose less than 12 mg in the core DB study. No titration was necessary for subjects who had achieved a daily dose of perampanel 12 mg in the core DB study. If additional dose adjustment was necessary during the Conversion Period, the site contacted the IVRS for dosing instructions, which may have lengthened the duration of the Conversion Period by 2 or 3 weeks. At the end of the Conversion Period, sites registered each subject MTD dose with the IVRS, who then informed the site of the subject current dose. The open-label Maintenance Period began at completion of the blinded Conversion Period. Subjects remained on the dose achieved at the end of the Conversion Period unless dose titration for tolerability and/or efficacy reasons was necessary. During the open-label Maintenance Period, subjects were treated with the perampanel dose that provided the best combination of individual efficacy and tolerability. Subjects who either withdrew from the study prematurely or completed the Maintenance Phase returned for a final visit at the end of the 4-week open-label Follow-up Phase. Visit 8 of the core DB between 8 and 56 days of entry into the OLE study were restarted on perampanel at a dose of 2 mg/day (i.e., same as for subjects who had been assigned to placebo in the core DB study). Subjects entered the OLE study on the concomitant AED regimen they were on during the core DB study. The dose(s) of the concomitant AED(s) could have been adjusted.**

***Number of Subjects*:**
Planned: Up to 1430 subjects. Enrolled as of interim data cutoff date: 1218 subjects, including 124 adolescent subjects, defined as those aged 12 to 17 years at the time of providing informed consent/assent in the core DBstudy.

***Diagnosis and Main Criteria for Inclusion*: Male and female subjects were eligible for this OLE study if they completed the DB Phase (Visit 8) of Study 304, 305, or 306 and showed compliance with the inclusion and exclusion criteria for that study (other than criteria related to seizure frequency); provided informed consent for participation in the OLE study; were currently receiving treatment with a stable dose of one to a maximum of three marketed AEDs (on a stable dose of two or three marketed AEDs in Lithuania); and were considered reliable and able to record seizure data and report AE information (or have a caretaker able to perform these duties).**

***Test Product, Dose and Mode of Administration*: Matching placebo 2-mg tablets, oral**

***Duration of Treatment*: The planned total duration of treatment during the OLE study is up to 5 years or until the product becomes available commercially (except in the United Kingdom and India where the total duration is 272 weeks [16-week Conversion Period + 256-week Maintenance Period]).**

***Criteria for Evaluation*:**
Efficacy:
Efficacy assessments included seizure counts from subject diaries. The key efficacy endpoints included the percent change in seizure frequency (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 seizure frequency during treatment per 28 days relative to baseline (responder).
Safety:
Safety assessments included examination of the incidence rates of AEs, SAEs, and withdrawals due to AEs; changes in vital signs and body weight; changes in laboratory test parameters; changes in withdrawal questionnaire responses, changes in quantitative ECG parameters and rates of abnormal overall ECG interpretations; and rates of concomitant medication use.

Statistical Methods: Efficacy analyses were based on the Full ITT Analysis Set, while safety analyses were based on the Safety Analysis Set. The Safety Analysis Set was defined as subjects who provided informed consent for the OLE study,

received at least one dose of perampanel in the OLE study, and had at least one post dose safety assessment in the OLE study (N = 1186 for overall population; N = 121 for adolescent population). Thirty-two subjects were enrolled and treated in the OLE study but were not included in the Safety Analysis Set as they did not have any post baseline safety data after the first OLE dose as of the interim cutoff date. The Full ITT Analysis Set was defined as subjects who provided informed consent for the OLE, received at least one dose of perampanel in the OLE study, and had valid seizure data during the perampanel treatment duration (DB and/or OLE studies) (N = 1207 for overall population; N = 122 for adolescents). As inclusion in the Full ITT Analysis Set for subjects treated in the OLE study was dependent on availability of seizure data during perampanel treatment in the DB and/or OLE studies, the number of subjects in this analysis set was higher than that in the Safety Analysis Set (which required availability of data in the OLE study) as of the interim cutoff date.

All data analyses were descriptive in nature, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints. Two general approaches were used to analyze efficacy data. The first examined seizure data by maximum perampanel dose received 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 DB study and used the Pre-randomization Phase of the core DB study as the baseline for evaluating change

The Pre-perampanel Baseline was defined as follows unless otherwise specified:

(1) for subjects who had been assigned to placebo treatment in the core DB study, the Pre-perampanel Baseline was computed from all data during the core DB study, and

(2) for subjects who had been assigned to perampanel in the core DB study, the Pre-perampanel Baseline was computed from the Pre randomization Phase of the core DB study. For all efficacy analyses, the perampanel treatment duration consisted of (1) the DB (Titration + Maintenance Periods) plus the OLE (Conversion + Maintenance Periods) for subjects assigned to perampanel in the core DB study and who had a ≤ 14-day gap in perampanel exposure between the DB and OLE studies; (2) the OLE Treatment Phase for subjects assigned to perampanel in the core DB study and who had a > 14-day gap in perampanel exposure between the DB and OLE studies; or (3) the OLE Treatment Phase for subjects assigned to placebo in the core DB study. For analyses using the Pre-randomization Phase of the core DB study for determining baseline seizure frequency, efficacy data were summarized by randomized treatment group in the core DB study for the DB Titration Period, DB Maintenance Period, OLE Conversion Period, and by 13-week intervals during the OLE Maintenance Period.

Additional summaries of the efficacy endpoints were provided for subgroups defined by age (<18, 18-64, and ≥65 years), sex, race (White, Asian or Pacific Islander, and Other), and number of AEDs (one, two, three) at DB Baseline. Summaries of the key efficacy endpoints were also examined for the subgroup of adolescent subjects. Subgroup analyses were performed using both efficacy analysis approaches (i.e., using Pre-perampanel Baseline and Pre-randomization Phase Baseline). Safety data were summarized by maximum daily dose (defined as <4 mg/day, 4 mg/day, >4 to 8 g/day, and >8 or 12 mg/day) and included data from the entire perampanel treatment duration. The perampanel treatment duration for AE analyses was defined as all exposure to perampanel in the core DB study and current OLE study. The perampanel treatment duration for all other safety endpoints was similar to that specified for the efficacy analyses, except that for subjects assigned to perampanel treatment in the core DB study who had a > 14-day gap in exposure between the core and current OLE study, the treatment duration was defined as the either the DB or OLE treatment phase, whichever was longer. Safety endpoints were also summarized for the subgroup of adolescent subjects.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication proposed for perampanel in this application is for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

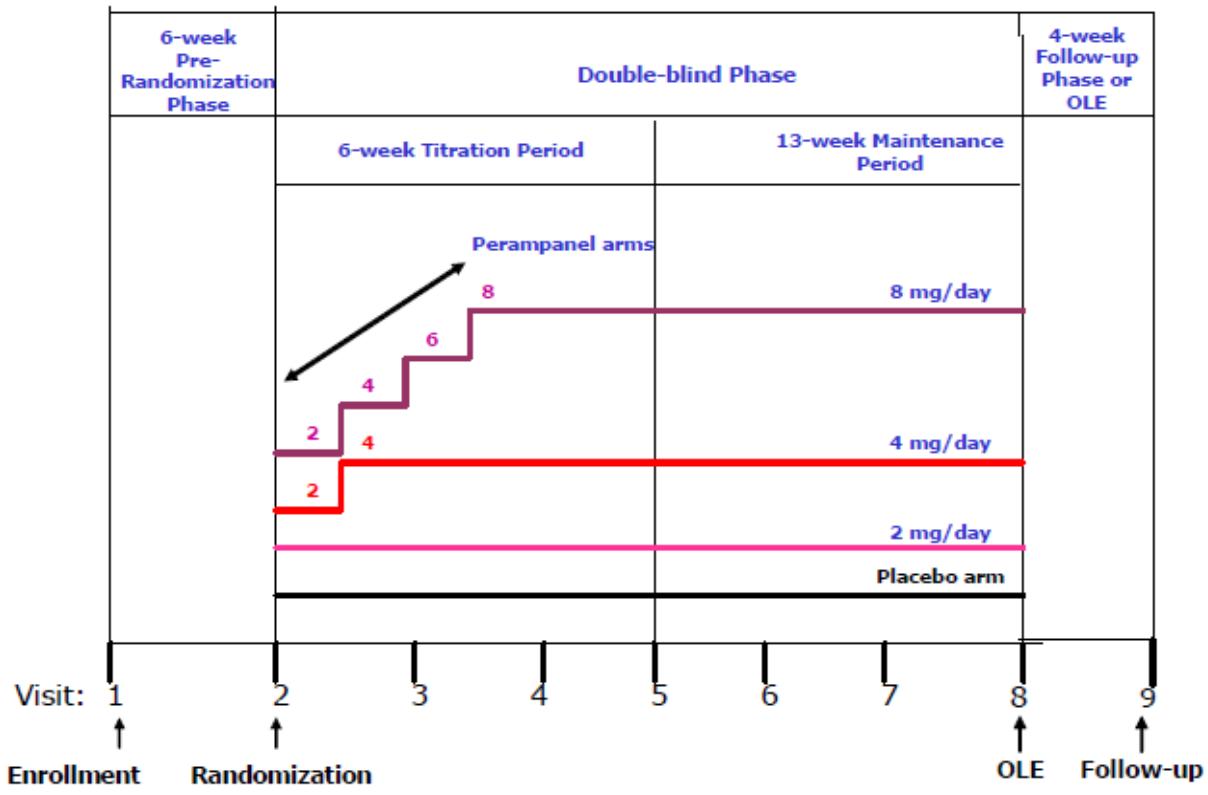
6.1.1 Methods

The three adequate and well-controlled Phase 3 studies of perampanel as adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalized seizures, were similar in design. Studies 306, 305, and 304 were randomized, double-blind, placebo-controlled, parallel-group, multicenter investigations of the efficacy, safety, and tolerability of fixed doses of perampanel given as adjunctive therapy (one to three concomitant AEDs) in subjects aged 12 years and older (18 years for sites in some countries). The controlled Phase 3 studies differed in the fixed doses of perampanel evaluated.

In Study 306, perampanel doses of 2 mg, 4 mg, and 8 mg once daily were compared to placebo.

The study design for Study 306 is depicted in the figure below, supplied by the sponsor.

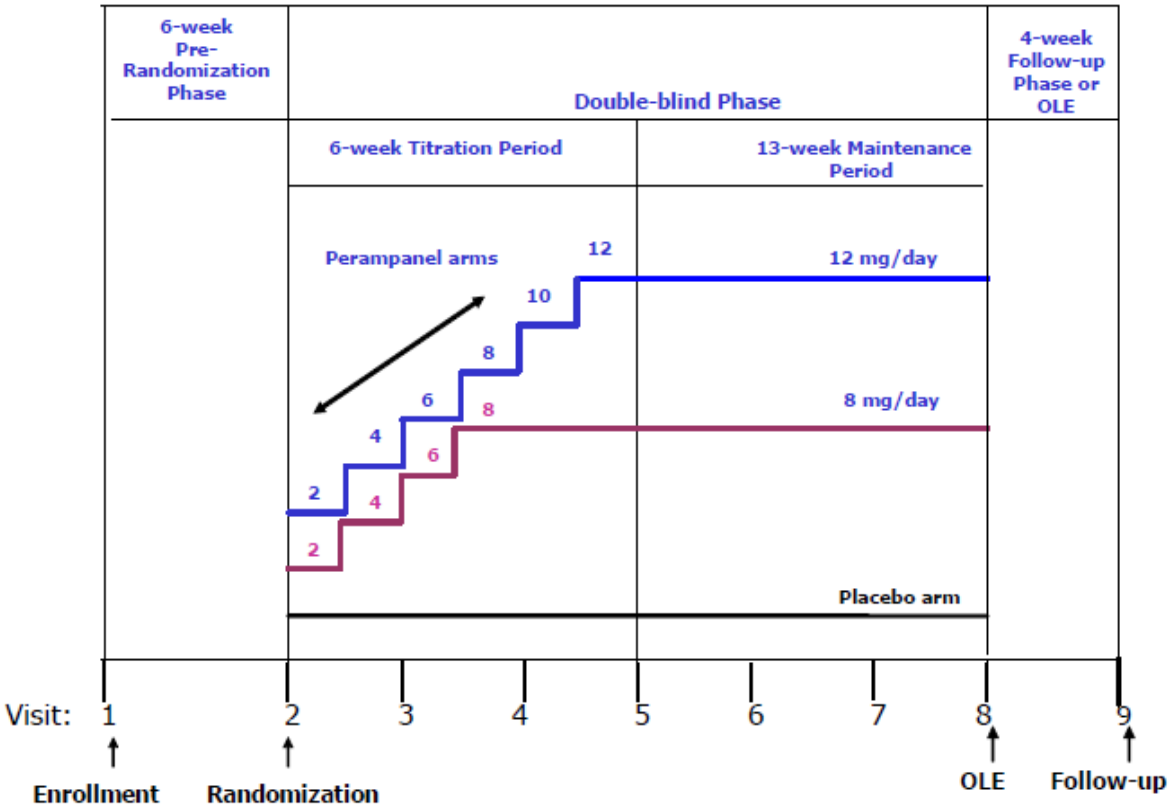
Figure 1 Study Design for Study 306



Studies 305 and 304 compared daily perampanel doses of 8 mg and 12 mg once daily to placebo. The doses evaluated in these studies were those expected to show efficacy based upon results of earlier Phase 2 studies.

The study design for Studies 305 and 304 are the same and are depicted in the figure below, supplied by the sponsor.

Figure 2 Study Design for Studies 305 and 304



Each of the Phase 3 studies consisted of three phases: Prerandomization Phase, including a Screening visit and a 6-week prospective Baseline Period; Double-blind Phase, consisting of a 6-week Titration Period and a 13-week Maintenance Period; and a Follow-up Phase of 4-weeks duration for subjects who withdrew prematurely or did not elect to enter the OLE study.

During the 6-week *Prerandomization Phase*, subjects who had provided written informed consent and who met study eligibility criteria at Visit 1 were required to record information about the number and type of seizures experienced in a daily diary. To be eligible to continue in the study, subjects must have experienced five or more partial-onset seizures (including at least two partial-onset seizures per each 3-week period) during this 6-week study phase and must not have had a 25-day period without seizures. Concomitant AED therapy must have remained unchanged during this study phase.

The *Double-blind Phase* was 19 weeks in duration and included Titration and Maintenance Periods. Subjects who met seizure frequency and type criteria during the Prerandomization Phase were randomly assigned with equal probability to receive study medication (placebo or 2, 4, or 8 mg perampanel in Study 306; placebo or 8 or 12 mg perampanel in Studies 305 and 304), administered once daily at bedtime with food. During the 6-week Titration Period a subject's dosage was increased in 2-mg increments on a weekly basis until the target dose was achieved. During the 13-week Maintenance Period subjects continued treatment with the randomly-assigned study medication in a blinded fashion. Subjects continued to take their baseline AED medication regimen throughout the Double-blind Phase and no changes to the concomitant AEDs were permitted. Down-titration of study medication was permitted during the Double-blind Phase for subjects experiencing intolerable adverse events; more than one down-titration was discouraged and the dose was to be increased again as soon as tolerability improved. Subjects who could not tolerate study drug (2 mg perampanel or placebo) by the end of the Titration Period were withdrawn from the study. Subjects who completed the Double-blind Phase could enter the OLE Study 307 and receive treatment with open-label perampanel.

Subjects who did not elect to enroll in the OLE study or who withdrew prematurely during the Double-blind Phase entered the 4-week *Follow-up Phase*. Study medication was discontinued at the start of this phase (i.e., there was no downward titration of study drug). Although subjects did not receive study medication during the Follow-up Phase, subjects and study sites remained blinded to the identity of the study medication received during the Double-blind Phase.

6.1.2 Demographics

For all three studies, the overall proportion of males and females was approximately equivalent. Between 8.5% and 11.4% of each study population were less than 18 years of age. Only a small minority (1.4% to 3.1%) of subjects in each study were 65 years of age or older. The controlled Phase 3 studies differed in the geographic location of the study sites which resulted in differences seen in the racial distribution of subjects between these studies. In each study, however, the majority of subjects were White (≥65%).

The geographic distribution of sites randomizing subjects in Studies 306, 305, and 304 is shown in the sponsor's table below.

Table 10 The geographic distribution of sites randomizing subjects in Studies 306, 305, and 304

Geographic Region	Study E2007-G000-306	Study E2007-G000-305	Study E2007-G000-304
All Sites, N	712	389	390
North America, n (%)	0	91 (23.4)	228 (58.5)
United States, n (%)	0	91 (23.4)	203 (52.1)
Europe, n (%)	416 (58.4)	241 (62.0)	0
Asia Pacific, n (%)	241 (33.8)	38 (9.8)	0
Central/South America, n (%)	0	0	162 (41.5)
Rest of World, n (%)	55 (7.7)	19 (4.9)	0

Source: 306, Table 14.1.2.4; 305, Table 14.1.2.4; 304, Table 14.1.2.4.
N (n) = number of subjects.
Percentages are based on the total number of randomized subjects.
North America includes Canada and US.
Europe includes Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Israel, Italy, Lithuania, Latvia, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Spain, Ukraine, and United Kingdom.
Asia Pacific includes China, Hong Kong, India, Korea, Malaysia, Philippines, Taiwan, and Thailand.
Central/South America includes Argentina, Chile, and Mexico.
Rest of World includes Australia and South Africa.

The important demographic characteristics for each of the 3 Phase 3 studies are summarized in the sponsor's table below.

Table 11 The important demographic characteristics for each of the 3 Phase 3 studies

	Placebo	Perampanel					Overall Total
		2 mg	4 mg	8 mg	12 mg	Total	
Study E2007-G000-306							
N	185	180	172	169		521	706
Sex, male, n (%)	95 (51.4)	85 (47.2)	88 (51.2)	77 (45.6)		250 (48.0)	345 (48.9)
Mean (SD) age[a] (years)	33.4 (12.55)	33.8 (13.62)	33.6 (12.19)	34.6 (12.77)		34.0 (12.87)	33.8 (12.78)
Age category[a], n (%)							
< 18 years	14 (7.6)	21 (11.7)	13 (7.6)	12 (7.1)		46 (8.8)	60 (8.5)
18 – 64 years	169 (91.4)	156 (86.7)	158 (91.9)	153 (90.5)		467 (89.6)	636 (90.1)
65+ years	2 (1.1)	3 (1.7)	1 (<1)	4 (2.4)		8 (1.5)	10 (1.4)
Race, n (%)							
White	119 (64.3)	119 (66.1)	105 (61.0)	116 (68.6)		340 (65.3)	459 (65.0)
Black or African/American	0	0	0	0		0	0
Asian	34 (18.4)	35 (19.4)	37 (21.5)	28 (16.6)		100 (19.2)	134 (19.0)
Chinese/Japanese	31 (16.8)	25 (13.9)	29 (16.9)	25 (14.8)		79 (15.2)	110 (15.6)
Other[b]	1 (< 1)	1 (< 1)	1 (< 1)	0		2 (< 1)	3 (< 1)
Study E2007-G000-305							
N	136			129	121	250	386
Sex, Male, n (%)	71 (52.2)			65 (50.4)	50 (41.3)	115 (46.0)	186 (48.2)
Mean (SD) age[a] (years)	34.4 (13.62)			36.7 (14.35)	35.5 (14.12)	36.1 (14.22)	35.5 (14.02)
Age category[a], n (%)							
< 18 years	17 (12.5)			17 (13.2)	10(8.3)	27 (10.8)	44 (11.4)
18 – 64 years	118 (86.8)			109 (84.5)	109 (90.1)	218 (87.2)	336 (87.0)
65+ years	1 (< 1)			3 (2.3)	2 (1.7)	5 (2.0)	6 (1.6)
Race, n (%)							
White	115 (84.6)			107 (82.9)	100 (82.6)	207 (82.8)	322 (83.4)
Black or African/American	1 (< 1)			2 (1.6)	1 (< 1)	3 (1.2)	4 (1.0)
Asian	12 (8.8)			14 (10.9)	16 (13.2)	30 (12.0)	42 (10.9)
Chinese/Japanese	0			0	0	0	0
Other[b]	8 (5.8)			6 (4.7)	4 (3.3)	10 (4.0)	18 (4.6)
Study E2007-G000-304							
N	121			133	134	267	388
Sex, Male, n (%)	54 (44.6)			65 (48.9)	69 (51.5)	134 (50.2)	188 (48.5)
Mean (SD) age[a] (years)	35.6 (14.67)			35.8 (14.21)	36.7 (14.64)	36.2 (14.41)	36.0 (14.48)
Age category[a], n (%)							
< 18 years	14 (11.6)			15 (11.3)	10 (7.5)	25 (9.4)	39 (10.1)
18 – 64 years	102 (84.3)			116 (87.2)	119 (88.8)	235 (88.0)	337 (86.9)
65+ years	5 (4.1)			2 (1.5)	5 (3.7)	7 (2.6)	12 (3.1)
Race, n (%)							
White	103 (85.1)			115 (86.5)	116 (86.6)	231 (86.5)	334 (86.1)
Black or African/American	13 (10.7)			6 (4.5)	8 (6.0)	14 (5.2)	27 (7.0)
Asian	0			1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Chinese/Japanese	0			1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Other[b]	5 (4.1)			10 (7.5)	8 (6.0)	18 (6.7)	23 (5.9)

The subject's epilepsy history is summarized in the sponsor's table below for the Safety Analysis Set in each of the three controlled Phase 3 studies. Subjects in each controlled Phase 3 study had a long history of epilepsy with the mean time since diagnosis for the overall Safety Analysis Set being approximately 19 years for Study 306, 22 years for Study 305, and 24 years for Study 304. In each study, complex partial seizures were the most common seizure type. To qualify for enrollment in the Phase 3 studies, subjects had to have a documented occurrence of at least five partial-onset seizures during the 6-week Prerandomization Phase, with no seizure-free period exceeding 21 days. The median frequency of all partial seizures per 28 days during the Prerandomization Phase was generally consistent across treatment groups within each study: 9.33 to 10.93 in Study 306, 11.79 to 13.69 in Study 305, and 12.00 to 14.34 in Study 304.

Table 12 Subject's epilepsy history

	Placebo	Perampanel					Overall Total
		2 mg	4 mg	8 mg	12 mg	Total	
Study E2007-G000-306							
N	185	180	172	169		521	706
Time since diagnosis (months)							
n	185	180	171	168		519	704
Mean (SD)	209.9 (128.10)	232.4 (145.20)	236.9 (145.32)	239.4 (142.92)		236.1 (144.26)	229.2 (140.58)
Minimum, maximum	23, 608	6, 600	6, 652	7, 760		6, 760	6, 760
Seizure type, n (%)							
Simple partial without motor signs	52 (28.1)	53 (29.4)	48 (27.9)	57 (33.7)		158 (30.3)	210 (29.7)
Simple partial with motor signs	55 (29.7)	53 (29.4)	54 (31.4)	51 (30.2)		158 (30.3)	213 (30.2)
Complex partial	155 (83.8)	153 (85.0)	147 (85.5)	138 (81.7)		438 (84.1)	593 (84.0)
Complex partial with 2nd generalized	136 (73.5)	115 (63.9)	119 (69.2)	117 (69.2)		351 (67.4)	487 (69.0)
Study E2007-G000-305							
N	136			129	121	250	386
Time since diagnosis (months)							
n	136			129	121	250	386
Mean (SD)	264.2 (155.30)			270.3 (163.36)	255.9 (158.64)	263.3 (160.93)	263.6 (158.77)
Minimum, maximum	9, 819			26, 743	23, 707	23, 743	9, 819
Seizure type, n (%)							
Simple partial without motor signs	48 (35.3)			49 (38.0)	36 (29.8)	85 (34.0)	133 (34.5)
Simple partial with motor signs	30 (22.1)			39 (30.2)	38 (31.4)	77 (30.8)	107 (27.7)
Complex partial	114 (83.8)			114 (88.4)	100 (82.6)	214 (85.6)	328 (85.0)
Complex partial with 2nd generalized	95 (69.9)			90 (69.8)	77 (63.6)	167 (66.8)	262 (67.9)
Study E2007-G000-304							
N	121			133	134	267	388
Time since diagnosis (months)							
n	121			133	133	266	387
Mean (SD)	289.6 (154.37)			282.8 (162.24)	279.5 (172.44)	281.1 (167.11)	283.8 (163.08)
Minimum, maximum	23, 719			11, 796	19, 797	11, 797	11, 797
Seizure type, n (%)							
Simple partial without motor signs	48 (39.7)			50 (37.6)	45 (33.6)	95 (35.6)	143 (36.9)
Simple partial with motor signs	41 (33.9)			47 (35.3)	40 (29.9)	87 (32.6)	128 (33.0)
Complex partial	107 (88.4)			116 (87.2)	122 (91.0)	238 (89.1)	345 (88.9)
Complex partial with 2nd generalized	87 (71.9)			91 (68.4)	101 (75.4)	192 (71.9)	279 (71.9)

Source: 306, Table 14.1.6.1; 305, Table 14.1.6.1; 304, Table 14.1.6.1.
N (n) = number of subjects; SD = standard deviation; 2nd = secondarily.
Shaded area indicates perampanel dose was not evaluated in a particular study.
Percentages are based on the total number of randomized and treated subjects in relevant treatment group.

The subject's in each of these Phase 3 studies were permitted to receive treatment with up to three concomitant AEDs. The distribution of the number of concomitant AEDs taken at baseline is summarized by treatment group in the sponsor's table below. Also summarized in this table are the most common concomitant AEDs (i.e., those received by 10% or more of the total Safety Analysis set for each study). Results for the controlled Phase 3 studies were consistent in showing that only a minority of subjects (10.9% to 15.5%) were receiving a single co-administered AED at baseline. The proportion of subjects receiving three concomitant AEDs was somewhat higher for Studies 306 (37.1%) and 305 (38.6%) than for Study 304 (28.9%). Carbamazepine, lamotrigine, levetiracetam, and valproic acid were the most common co-administered AEDs in each Phase 3 study. Results of drug-drug interaction studies, coupled with findings from population-PK modeling using data from the Phase 3 studies, suggest that perampanel is associated with few potential drug interactions, particularly with other AEDs. The AEDs shown to be statistically significant inducers of perampanel were carbamazepine, oxcarbazepine, and phenytoin.

For more detailed discussion refer to section 6.1.7.

Table 13 Subject's background AED therapy in each of the Phase 3 studies

	Placebo	Perampanel					Overall Total
		2 mg	4 mg	8 mg	12 mg	Total	
Study E2007-G000-306							
N	185	180	172	169		521	706
Total AEDs at baseline,[a] n(%)							
Only 1 AED	28 (15.1)	30 (16.7)	19 (11.0)	27 (16.0)		76 (14.6)	104 (14.7)
Exactly 2 AEDs	90 (48.6)	80 (44.4)	88 (51.2)	82 (48.5)		250 (48.0)	340 (48.2)
Exactly 3 AEDs	67 (36.2)	70 (38.9)	65 (37.8)	60 (35.5)		195 (37.4)	262 (37.1)
Common AEDs at baseline,[b] n (%)							
Carbamazepine	64 (34.6)	58 (32.2)	56 (32.6)	53 (31.4)		167 (32.1)	231 (32.7)
Lamotrigine	57 (30.8)	56 (31.1)	68 (39.5)	66 (39.1)		190 (36.5)	247 (35.0)
Levetiracetam	44 (23.8)	48 (26.7)	45 (26.2)	45 (26.6)		138 (26.5)	182 (25.8)
Oxcarbazepine	36 (19.5)	35 (19.4)	25 (14.5)	34 (20.1)		94 (18.0)	130 (18.4)
Topiramate	51 (27.6)	38 (21.1)	40 (23.3)	40 (23.7)		118 (22.6)	169 (23.9)
Valproic acid	77 (41.6)	80 (44.4)	75 (43.6)	63 (37.3)		218 (41.8)	295 (41.8)
Study E2007-G000-305							
N	136			129	121	250	386
Total AEDs at baseline,[a] n(%)							
Only 1 AED	17 (12.5)			16 (12.4)	9 (7.4)	25 (10.0)	42 (10.9)
Exactly 2 AEDs	64 (47.1)			68 (52.7)	63 (52.1)	131 (52.4)	195 (50.5)
Exactly 3 AEDs	55 (40.4)			45 (34.9)	49 (40.5)	94 (37.6)	149 (38.6)
Common AEDs at baseline,[b] n(%)							
Carbamazepine	43 (31.6)			43 (33.3)	47 (38.8)	90 (36.0)	133 (34.5)
Clobazam	18 (13.2)			14 (10.9)	17 (14.0)	31 (12.4)	49 (12.7)
Lamotrigine	37 (27.2)			40 (31.0)	27 (22.3)	67 (26.8)	104 (26.9)
Levetiracetam	52 (38.2)			49 (38.0)	46 (38.0)	95 (38.0)	147 (38.1)
Oxcarbazepine	23 (16.9)			25 (19.4)	24 (19.8)	49 (19.6)	72 (18.7)
Topiramate	24 (17.6)			25 (19.4)	22 (18.2)	47 (18.8)	71 (18.4)
Valproic acid	32 (23.5)			25 (19.4)	26 (21.5)	51 (20.4)	83 (21.5)
Zonisamide	19 (14.0)			12 (9.3)	11 (9.1)	23 (9.2)	42 (10.9)
Study E2007-G000-304							
N	121			133	134	267	388
Total AEDs at baseline[a] n (%)							
Only 1 AED	15 (12.4)			26 (19.5)	19 (14.2)	45 (16.9)	60 (15.5)
Exactly 2 AEDs	64 (52.9)			70 (52.6)	82 (61.2)	152 (56.9)	216 (55.7)
Exactly 3 AEDs	42 (34.7)			37 (27.8)	33 (24.6)	70 (26.2)	112 (28.9)
Common AEDs at baseline,[b] n (%)							
Carbamazepine	36 (29.8)			42 (31.6)	49 (36.6)	91 (34.1)	127 (32.7)
Clonazepam	22 (18.2)			13 (9.8)	8 (6.0)	21 (7.9)	43 (11.1)
Lamotrigine	31 (25.6)			40 (30.1)	36 (26.9)	76 (28.5)	107 (27.6)
Levetiracetam	29 (24.0)			37 (27.8)	41 (30.6)	78 (29.2)	107 (27.6)
Oxcarbazepine	29 (24.0)			19 (14.3)	20 (14.9)	39 (14.6)	68 (17.5)
Phenytoin	17 (14.0)			18 (13.5)	16 (11.9)	34 (12.7)	51 (13.1)
Topiramate	15 (12.4)			16 (12.0)	23 (17.2)	39 (14.6)	54 (13.9)
Valproic acid	31 (25.6)			32 (24.1)	37 (27.6)	69 (25.8)	100 (25.8)
Zonisamide	11 (9.1)			17 (12.8)	12 (9.0)	29 (10.9)	40 (10.3)

Source: 306, Table 14.1.6.2.1; 306, Table 14.1.6.2.2; 305, Table 14.1.6.2.1; 305, Table 14.1.6.2.2; 304, Table 14.1.6.2.1; 304, Table 14.1.6.2.2.
AED = anti-epileptic drug; N (n) = number of subjects.
Shaded area indicates perampanel dose was not evaluated in a particular study.
Percentages are based on the total number of randomized and treated subjects in relevant treatment group.
a: The subjects are classified by the number of anti-epileptic drugs used at baseline.
b: AEDs used at baseline in at least 10% of subjects in the Overall Total group.

6.1.3 Subject Disposition

The number of randomized and treated subjects who completed the study and the reasons for premature discontinuation from double-blind treatment are summarized for Studies 306, 305, and 304 in the sponsor's table below.
For each Phase 3 study, results were consistent in showing that the subject retention rate was relatively high and in a similar range for the placebo and 2 mg, 4 mg, and 8 mg perampanel treatment groups. In each of the three studies, the most common reasons for discontinuation for all treatment groups were adverse events and subject choice. In Studies 305 and 304, the percentage of subjects who completed study treatment was lower for the perampanel 12 mg group than for either the placebo or perampanel 8 mg group, with the difference due to a higher rate of discontinuation due to adverse events in the 12 mg group. In each study, ≤1% of all subjects in each study were discontinued due to a lack of therapeutic effect. The overall percentage of subjects in the combined perampanel treatment group who completed the double-blind study was comparable among those whose background AED therapy included carbamazepine (87.2%), oxcarbazepine (86.3%), lamotrigine (86.7%), levetiracetam (84.8%), topiramate (86.4%), or valproic acid (87.7%).

Table 14 Subject Disposition

	Placebo	Perampanel					Overall Total
		2 mg	4 mg	8 mg	12 mg	Total	
Study E2007-G000-306							
Randomized and treated, N	185[a]	180[a]	172	169		521	706
Completed study[b], n (%)	166 (89.7)	154 (85.6)	158 (91.9)	145 (85.8)		457 (87.7)	623 (88.2)
Discontinued prematurely, n (%)	19 (10.3)	26 (14.4)	14 (8.1)	24 (14.2)		64 (12.3)	83 (11.8)
Primary reason for discontinuation							
Adverse event	6 (3.2)	10 (5.6)	5 (2.9)	11 (6.5)		26 (5.0)	32 (4.5)
Subject choice	8 (4.3)	9 (5.0)	8 (4.7)	8 (4.7)		25 (4.8)	33 (4.7)
Lost to follow-up	4 (2.2)	1 (< 1)	0	1 (< 1)		2 (< 1)	6 (< 1)
Inadequate therapeutic effect	0	3 (1.7)	0	1 (< 1)		4 (< 1)	4 (< 1)
Administrative/Other	1 (< 1)	3 (1.7)	1 (<1)	3 (1.8)		7(1.3)	8 (1.1)
Study E2007-G000-305							
Randomized and treated, N	136			129	121	250	386
Completed study[b], n (%)	120 (88.2)			108 (83.7)	93 (76.9)	201 (80.4)	321 (83.2)
Discontinued prematurely, n (%)	16 (11.8)			21 (16.3)	28 (23.1)	49 (19.6)	65 (16.8)
Primary reason for discontinuation							
Adverse event	4 (2.9)			11 (8.5)	23 (19.0)	34 (13.6)	38 (9.8)
Subject choice	6 (4.4)			7 (5.4)	4 (3.3)	11 (4.4)	17 (4.4)
Inadequate therapeutic effect	1 (<1)			0	1 (< 1)	1 (< 1)	2 (< 1)
Progressive disease[c]	1 (<1)			0	0	0	1 (< 1)
Administrative/Other	4 (2.9)			3 (2.3)	0	3 (1.2)	7 (1.8)
Study E2007-G000-304							
Randomized and treated, n	121			133[a]	134[a]	267	388
Completed Study[b], n (%)	106 (87.6)			114 (85.7)	100 (74.6)	214 (80.1)	320 (82.5)
Discontinued prematurely, n (%)	15 (12.4)			19 (14.3)	34 (25.4)	53 (19.9)	68 (17.5)
Primary reason for discontinuation							
Adverse event	7 (5.8)			9 (6.8)	24 (17.9)	33 (12.4)	40 (10.3)
Subject choice	3 (2.5)			7 (5.3)	4 (3.0)	11 (4.1)	14 (3.6)
Lost to follow-up	0			2 (1.5)	0	2 (< 1)	2 (< 1)
Inadequate therapeutic effect	2 (1.7)			0	2 (1.5)	2 (< 1)	4 (1.0)
Administrative/Other	3 (2.5)			1 (< 1)	4 (3.0)	5 (1.9)	8 (2.1)

Source: 306, Table 14.1.2.1; 305, Table 14.1.2.1; 304, Table 14.1.2.1.
N (n) = number of subjects.
Shaded area indicates perampanel dose was not evaluated in a particular study.
Percentages are based on the total number of randomized and treated subjects in relevant treatment group.
a: One subject was inappropriately randomized (see Section 10.1 of corresponding CSR).
b: As reported on the End of Study (Subject Disposition) case report form, study completion.
c: Subject 24125001 was mistakenly indicated as having progression of disease instead of progression of seizures.

6.1.4 Analysis of Primary Endpoints

The primary efficacy assessment was based on the following:

- **Primary efficacy endpoint: Percent change in seizure frequency per 28 days during the double-blind phase from baseline.**
- **Primary analysis: An ANCOVA was performed on the rank-transformed % change data (both the baseline and % change seizure frequencies per 28 days). The model includes treatment and pooled countries as factors, and the ranked baseline as a covariate.**
- **Multiplicity adjustment for multiple comparisons: A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary endpoint for different dose groups: first test a lower dose, if the lower dose demonstrates superiority, then the next higher dose will be tested.**

The primary efficacy endpoint was based on seizure counts derived from the subject diaries. Subjects, or a designated caregiver, completed a daily paper diary on which they recorded seizure counts and type throughout the entire study. All simple partial seizures (with or without motor signs), complex partial seizures, and complex partial seizures with secondary generalization were recorded. To try and ensure correct seizure classification, the investigator reviewed the subject diary with the subject at both Visits 1 and 2. The seizure diary was reviewed for completeness at each visit, and subjects were counseled if diary compliance was unsatisfactory.

The prespecified primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The sponsor's table below summarizes the percent change in seizure frequency per 28 days during the Double-blind Phase relative to the Prerandomization Phase for the Full ITT Analysis Set for each controlled Phase 3 study.

The median percent reductions in seizure frequency per 28 days during the Double-blind Phase relative to Prerandomization for the Full ITT Analysis Set were larger in all perampanel treatment groups than in the respective placebo groups, except for the 2 mg group in Study 306. In all 3 studies the treatment differences relative to placebo in the primary efficacy variable for the Full ITT Analysis Set were statistically significant for the 4 mg, 8 mg, and 12 mg perampanel treatment groups based on the rank ANCOVA. These results were

supported by the log transformation-based ANCOVA, which also showed statistical separation from placebo for all perampanel dose groups except for the 2-mg group in Study 306, as detailed in the sponsor's table below.

Table 15 Efficacy Results for all three Phase 3 Studies

Study/Parameter Statistics	Placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg	Perampanel 12 mg
Study E2007-G000-306					
N	184	180	172	169	
Prerandomization seizure frequency					
Median	9.33	10.12	10.02	10.93	
Percent change during Double-blind Phase from Prerandomization					
Median	-10.69	-13.63	-23.33	-30.80	
Median difference to placebo[a]		-4.36	-13.71	-20.13	
(95% CI)		(-14.091, 5.227)	(-23.306, -4.500)	(-29.656, -10.425)	
P value vs. placebo[b]		0.4197	0.0026	<0.0001	
Study E2007-G000-305					
N	136			129	121
Prerandomization seizure frequency					
Median	11.79			13.02	13.69
Percent change during Double-blind Phase from Prerandomization					
Median	-9.72			-30.52	-17.57
Median difference to placebo[a]				-19.10	-13.69
(95% CI)				(-29.169, -8.447)	(-25.198, -2.257)
P value vs. placebo[b]				0.0008	0.0105
Study E2007-G000-304					
N	121			133	133
Prerandomization seizure frequency					
Median	13.66			14.34	12.00
Percent Change during Double-blind Phase from Prerandomization					
Median change	-20.95			-26.34	-34.49
Median difference to placebo[a]				-13.53	-14.20
(95% CI)				(-26.172, -1.944)	(-25.030, -2.729)
P value vs. placebo[b]				0.0261	0.0158

Source: 306, Table 14.2.1.1.6.1; 305, Table 14.2.1.1.1.1; 304, Table 14.2.1.1.6.1.
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; N = number of subjects; vs = versus.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: For analysis windows, the *P* value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as covariate. The Prerandomization and post randomization efficacy measurements are rank transformed separately.

Primary Efficacy Result *Study 306*

Efficacy was derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment

and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate.

To help determine the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group (2 mg for 306) was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 306.

Table 16 Decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 306

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 306				
Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	182	177	168	166
Median	-10.11	-14.13	-23.99	-31.34
Median Difference to Placebo (95% CI)		-23.27 (-63.59, 17.05)	-69.92 (-110.84, -29)	-92.45 (-133.52, -51.38)
P-value		0.26	0.0008	<0.0001

There were no US sites in this study, which was conducted at 116 sites in Australia, Bulgaria, China, Czech Republic, Estonia, Germany, Hong Kong, Hungary, India, Italy, Latvia, Lithuania, Malaysia, Philippines, Poland, Portugal, Romania, Serbia, South Korea, Spain, Taiwan, Thailand and Ukrane.

In Europe, 4 and 8mg doses were effective and in Asia 8mg was effective while there was no effect in Russia.

The table below, jointly prepared with statistician Dr. Cherry Liu, details these findings.

Table 17 Geographic Differences in Seizure Frequency in Study 306

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Region, Study 306					
Region	Statistic	Placebo	Perampanel		
			2 mg	4 mg	8 mg
Europe	n	103	101	96	100
	Median	-12.66	-13.72	-25.24	-34.89
	Median Difference to Placebo (95% CI)		-25.36 (-79.68, 28.96)	-87.37 (-142.53, -32.2)	-96.71 (-151.18, -42.26)
	P-value		0.36	**0.002**	**0.0005**
Asia	n	62	60	60	50
	Median	-8.12	-19.78	-23.45	-36.76
	Median Difference to Placebo (95% CI)		-46.76 (-116.87, 23.35)	-47.41 (-117.35, 22.52)	-116.73 (-190.24, -43.23)
	P-value		0.19	0.18	0.002
Russia	n	17	16	12	16
	Median	-3.28	14.61	-5.83	0.46
	Median Difference to Placebo (95% CI)		-23.27 (-63.59, 17.05)	-47.73 (-184.56, 89.1)	7.85 (-120.73, 136.44)
	P-value		0.26	0.49	0.9

*Statistically significant at α=0.05

The ITT analysis showed that only the two higher doses (4 and 8mg) seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. The subgroup analysis supports that the two higher doses were effective in the Europe and Asia region.

Primary Efficacy Result *Study 305*

Efficacy is derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate. To help evaluate the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 305.

Table 18 Primary Efficacy Results for Study 305

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 305			
Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	136	129	121
Median	-9.72	-30.52	-17.57
Median Difference to Placebo (95% CI)		-45.50 (-71.86, -19.14)	-35 (-61.74, -8.26)
P-value		0.0008	0.0105

As detailed in the table below, jointly produced with statistician Dr. Cherry Liu, efficacy was demonstrated in Europe only, while there was no statistically significant effect in the US, India and Russia. 84 sites were involved in Austria, Australia, Belgium, Germany, Finland, France, Greece, India, Israel, Italy, Netherlands, Russia, Sweden, South Africa, UK and US.

Table 19 Geographic Differences in Seizure Frequency in Study 305

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Region, Study 305				
Region	Statistic	Placebo	Perampanel	
			8 mg	12 mg
Europe	n	84	75	70
	Median	-2.11	-20.04	-14.88
	Median Difference to Placebo (95% CI)		-50.77 (-84.95, -16.6)	-44.08 (-78.87, -9.27)
	P-value		**0.004***	**0.013***
USA	n	33	31	27
	Median	-23.31	-41.64	-21.64
	Median Difference to Placebo (95% CI)		-35.62 (-86.35, 15.11)	-0.62 (-53.77, 52.53)
	P-value		0.17	0.98
India	n	10	14	14
	Median	-33.79	-45.42	-30.66
	Median Difference to Placebo (95% CI)		3.83 (-110.07, 117.73)	-1.09 (-106.76, 104.59)
	P-value		0.95	0.98
Russia	n	9	10	9
	Median	-5.63	-23.67	-31.02
	Median Difference to Placebo (95% CI)		-70.98 (-173.68, 31.72)	-75.84 (-175.16, 23.49)
	P-value		0.17	0.13

*Statistically significant at α=0.05

The ITT analysis showed that both doses, 8 and 12mg, seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. In this analysis, 8mg appears to be more efficacious than 12mg. The subgroup analysis showed that the efficacy was only demonstrated in Europe, but not other regions, including the USA.

Primary Efficacy Result *Study 304*

Efficacy is derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change

per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate to determine the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 304.

Table 20 Primary Efficacy Results for Study 304

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 304			
Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	121	133	133
Median	-20.95	-26.34	-34.49
Median Difference to Placebo (95% CI)		-13.53 (-26.17, -1.94)	-14.20 (-25.03, -2.73)
P-value		0.0261	0.0184

This study was conducted at 77 sites, in five countries, including Argentina, Canada, Chile, Mexico and the US. As detailed in the sponsor's table below, the greatest efficacy was demonstrated in North America, while there was no evidence of effectiveness in Central and South America where there was a high placebo rate.

Table 21 Geographic Differences in Seizure Frequency in Study 304

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Regions, Study 304				
Region	Statistic	Placebo	Perampanel	
			8 mg	12 mg
North America: CAN, USA	n	73	74	80
	Median	-11.34	-27.63	-36.91
	Median Difference to Placebo (95% CI)		-61.18 (-96.95, -25.41	-62.96 (-98.01, -27.91)
	P-value		**0.0009***	**0.0005***
Central & South America: ARG, CHI, MEX	n	48	59	53
	Median	-26.92	-24.88	20.73
	Median Difference to Placebo (95% CI)		14.69 (-27.94, 57.33)	14.72 (-28.91, 58.35)
	P-value		0.50	0.51
USA	n	66	64	72
	Median	-9.52	-25.38	-35.22
	Median Difference to Placebo (95% CI)		-30.94 (-50.46, -11.42	-37.06 (-56.04, -18.09)
	P-value		**0.002**	**0.0002**

*Statistically significant at α=0.05

The ITT analysis showed that both doses, 4 and 8mg, seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. A subgroup analysis demonstrates efficacy in North America, but not in Central and South America.

6.1.5 Analysis of Secondary Endpoints

The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was the percent change in the frequency of complex partial plus secondarily generalized seizures.

A responder was defined as a subject who experienced a 50% or greater reduction in seizure frequency per 28 days during the Maintenance Period (with LOCF imputation) relative to the Prerandomization Phase. The responder rate calculations were done using data from the Maintenance Period to avoid the potential confounding influences of dose titration. Results of the analysis of the responder rate for the Full ITT Analysis Set are summarized for each controlled Phase 3 study in the sponsor's table below.

Table 22 50% Responder Rate for all three Phase 3 Studies

Study Parameter/Statistics	Placebo	Perampanel			
		2 mg	4 mg	8 mg	12 mg
Study E2007-G000-306					
N	184	180	172	169	
Responder, n (%)	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)	
P value vs. placebo[a]		0.4863	0.0132	0.0003	
Study E2007-G000-305					
N	136			129	121
Responder, n (%)	20 (14.7)			43 (33.3)	41 (33.9)
P value vs.placebo[a]				0.0018	0.0006
Study E2007-G000-304					
N	121			133	133
Responder, n (%)	32 (26.4)			50 (37.6)	48 (36.1)
P value vs. placebo[a]				0.0760	0.0914

Source: 306, Table 14.2.2.3.5; 305, Table 14.2.2.3.5.1; Study 304, Table 14.2.2.3.5.1.
Shaded area indicates perampanel dose was not evaluated in a particular study.
CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; LOCF = last observation carried forward; N (n) = number of subjects; vs = versus.
a: The *P* value is based on non-missing values and is from the CMH test adjusted for pooled country.

In all three Phase 3 studies the responder rate was numerically greater for all perampanel dose groups than for the respective placebo group. The treatment

differences relative to placebo in the responder rate during the Maintenance Period for the Full ITT Analysis Set were statistically significant for the perampanel 4-mg and 8-mg groups in Study 306 and for the perampanel 8-mg and 12-mg groups in Study 305

While the responder rates for the perampanel 8-mg and 12-mg groups in Study 304 were similar to those for the 8 mg and 12 mg groups in Study 305, the responder rate in the placebo group was higher for Study 304 (26.4% in Study 304 versus 14.7% in Study 305). As a result, the treatment differences relative to placebo for the 8-mg and 12-mg groups in Study 304 did not achieve statistical significance (P = 0.0760 and P = 0.0914, respectively). The high placebo response in Study 304 appears to have been driven by data from sites in Central and South America (162 of 390 sites, 41.5%). When only data from North American sites were evaluated for this study, the responder rates during the Maintenance Period (LOCF) for the 8-mg and 12-mg perampanel groups were statistically significantly higher than those for the placebo group (P values of 0.0209 and 0.0169, respectively).

The median percent change in the frequency of complex partial plus secondarily generalized seizures during the Double-blind Phase relative to the Prerandomization Phase for the Full ITT Analysis Set is summarized for each controlled Phase 3 study in the sponsor's table below. The results for this seizure type were consistent with those for all seizures in demonstrating that the median percent reductions in the frequency per 28 days of these seizures during the Double-blind Phase (Full ITT Analysis Set) were statistically significantly larger in the perampanel 4 mg and 8 mg groups in Study 306, and in the 8 mg and 12 mg groups in Studies 305 and 304, than in the respective placebo group based on the rank ANCOVA.

Table 23 Median percent change in the frequency of complex partial plus secondarily generalized seizures during the Double-blind Phase in all three Phase 3 Studies

Study/Parameter Statistics	Placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg	Perampanel 12 mg
Study E2007-G000-306					
N	169	167	157	154	
Prerandomization seizure frequency					
Median	6.15	6.83	7.51	7.70	
Percent change during Double-blind Phase from Prerandomization					
Median	-17.63	-20.50	-31.18	-38.69	
Median difference to placebo[a]		-3.26	-14.40	-19.32	
(95% CI)		(-13.685, 7.395)	(-25.082, -3.496)	(-29.788, -8.625)	
P value vs. placebo[b]		0.6506	0.0070	0.0005	
Study E2007-G000-305					
N	126			119	113
Prerandomization seizure frequency					
Median	8.20			7.51	10.18
Percent change during Double-blind Phase from Prerandomization					
Median	-8.05			-32.72	-21.89
Median difference to placebo[a]				-23.07	-17.45
(95% CI)				(-34.798, -10.549)	(-29.269, -5.703)
P value vs. placebo[b]				0.0007	0.0045
Study E2007-G000-304					
N	110			120	120
Prerandomization seizure frequency					
Median	9.45			8.20	9.68
Percent Change during Double-blind Phase from Prerandomization					
Median change	-17.88			-33.03	-33.06
Median difference to placebo[a]				-20.37	-17.90
(95% CI)				(-33.164, -7.741)	(-30.313, -4.665)
P value vs. placebo[b]				0.0020	0.0081

Source: 306, Table 14.2.10.1; 305, Table 14.2.2.1.1; 304, Table .14.2.14.1.1.
ANCOVA = analysis of covariance; CI = confidence interval, ITT = intent-to-treat; N = number of subjects; vs = versus.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: For analysis windows, the P value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as covariate. The Prerandomization and post randomization efficacy measurements are rank transformed separately.

6.1.6 Other Endpoints

The primary (section 6.1.4) and secondary endpoints (section 6.1.5), and many of the exploratory endpoints, were based on seizure counts from subject diaries. Other exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.

Exploratory Endpoints

Change in the Number of Seizure-free Days

At baseline, the mean number of seizure-free days per 28 days was approximately 17 days in each treatment group for the ITT Analysis Set. In the Double-blind Phase, there were mean increases in the number of seizure-free days of 0.8 days in the placebo group, 1.5 days in the perampanel 2 mg group, 1.8 days in the perampanel 4 mg group, and 2.1 days in the perampanel 8 mg group. The P values for the comparison with placebo were 0.0965 for 2 mg, 0.0153 for 4 mg, and 0.0006 for 8 mg.

Percentage of Subjects Who Achieved Seizure-free Status

Among the subjects in the ITT Analysis Set with at least 28 days of treatment in the Maintenance Period, 7.0% of those in the placebo group, 9.1% of those in the 2 mg group, 9.3% of those in the 4 mg group, and 11.3% of those in the 8 mg group achieved seizure-free status during the last 28 days of treatment. The P values for the comparison with placebo were 0.5487, 0.5478, and 0.2416, respectively. Among those who completed the Maintenance Period, the percentages of subjects who achieved seizure-free status were 1.2% in the placebo group, 1.9% in the 2 mg group, 4.4% in the 4 mg group, and 4.8% in the 8 mg group. The P values for the comparison with placebo were 0.6745, 0.0972, and 0.0875, respectively.

Responder Rates for Complex Partial Seizures plus Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 24.0% in the placebo group, 27.4% in the 2 mg group, 35.9% in the 4 mg group, and 39.1% in the 8 mg group. The P values for the comparison with placebo were 0.4583 for 2 mg, 0.0183 for 4 mg, and 0.0048 for 8 mg.

Responder Rates for Secondarily Generalized Seizures

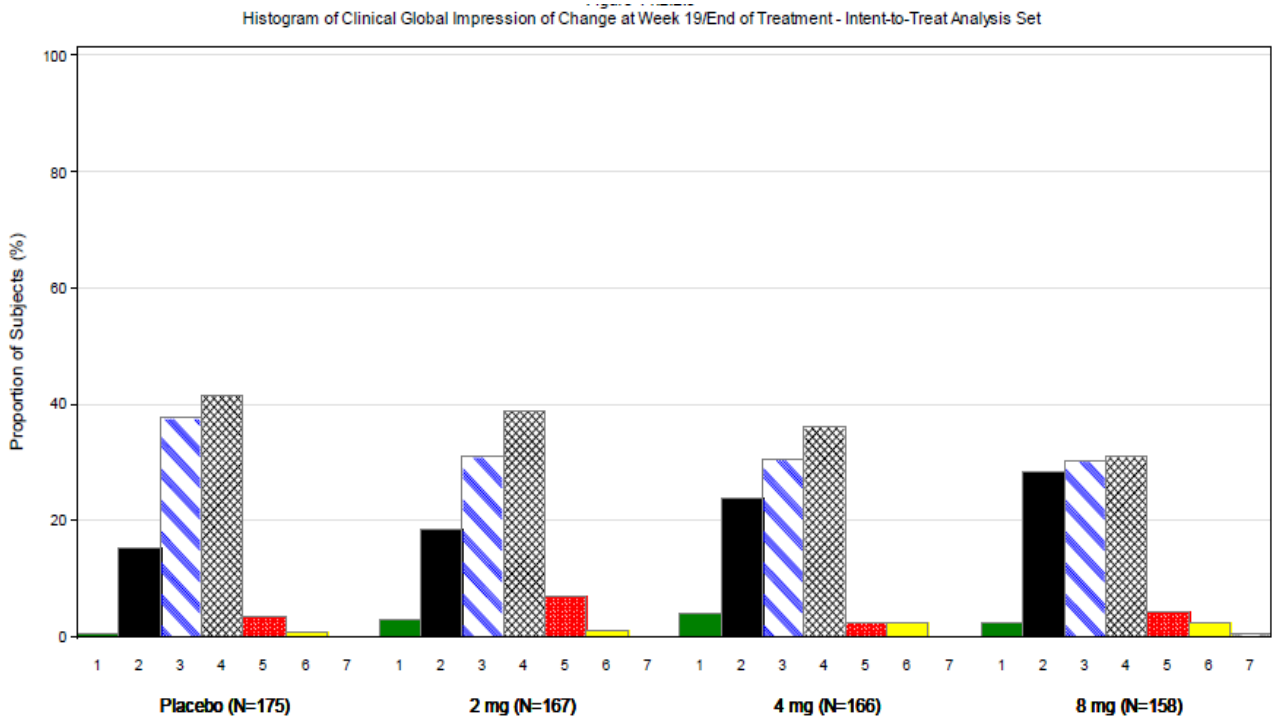
The responder rates during the Maintenance Period (LOCF) were 45.6% in the placebo group, 44.8% in the 2 mg group, 50.0% in the 4 mg group, and 61.7% in the 8 mg group. The P values for the comparison with placebo were 0.5373 for 2 mg, 0.7062 for 4 mg, and 0.2708 for 8 mg.

The following exploratory endpoints were similar in all three Phase 3 studies. Details are shown for Study 306 which appears representative of the others.

Clinical Global Impression of Change

The results for the Clinical Global Impression of Change in Study 306 are illustrated in the sponsor's figure below. At the end of treatment, 15.9% of the subjects in the placebo group, 21.3% of those in the 2 mg group, 28.1% of those in the 4 mg group, and 30.4% of those in the 8 mg group were considered much or very much improved by the investigators; the remaining subjects were rated minimally improved to very much worse. The P values for the differences relative to placebo were 0.2093 for 2 mg, 0.0063 for 4 mg, and 0.0013 for 8 mg.

Figure 3 Clinical Global Impression of Change in Study 306

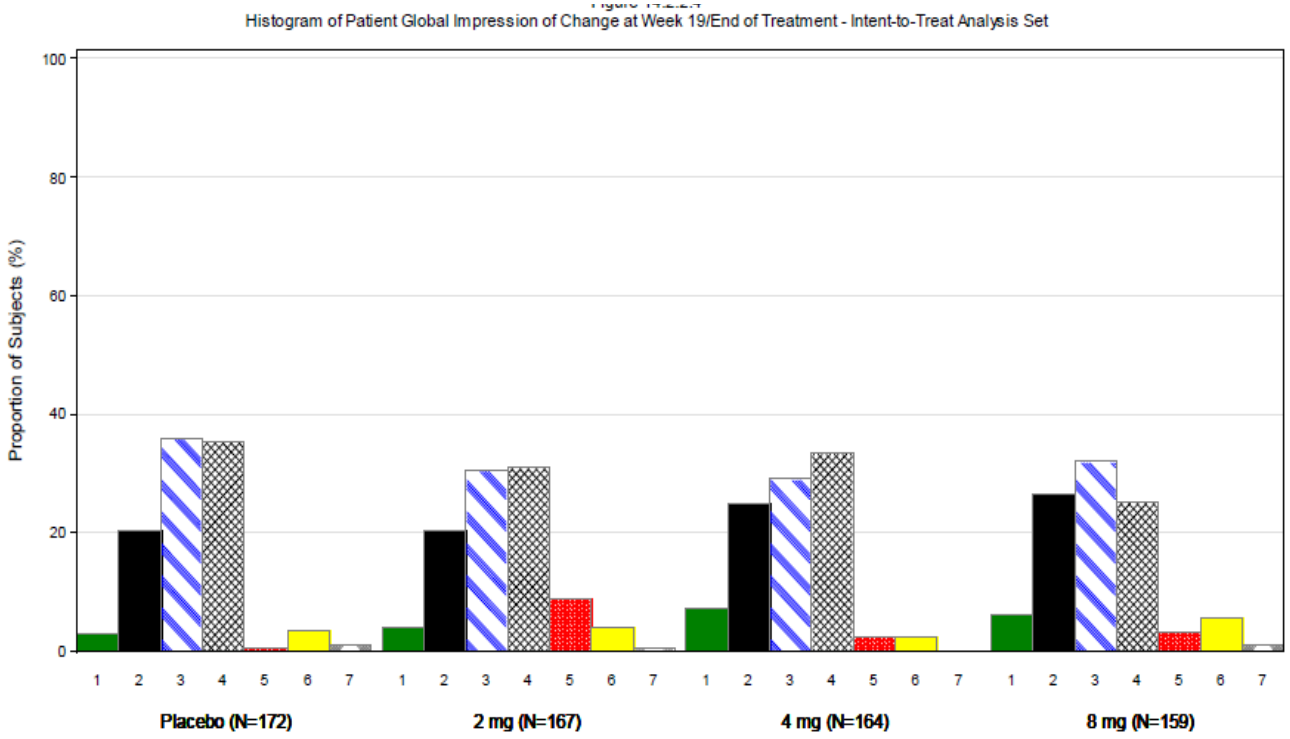


1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No Change, 5=Minimally worse, 6=Much worse, 7=Very much worse

Patient Global Impression of Change

The results for the Patient Global Impression in Study 306 are illustrated in the sponsor's figure below. At the end of treatment, 23.1% of the subjects in the placebo group, 24.3% of those in the 2 mg group, 32.1% of those in the 4 mg group, and 32.3% of those in the 8 mg group considered themselves much or very much improved; the remaining subjects considered themselves minimally improved to very much worse. The P values for the differences relative to placebo were 0.8039 for 2 mg, 0.0618 for 4 mg, and 0.0529 for 8 mg.

Figure 4 Patient Global Impression of Change in Study 306

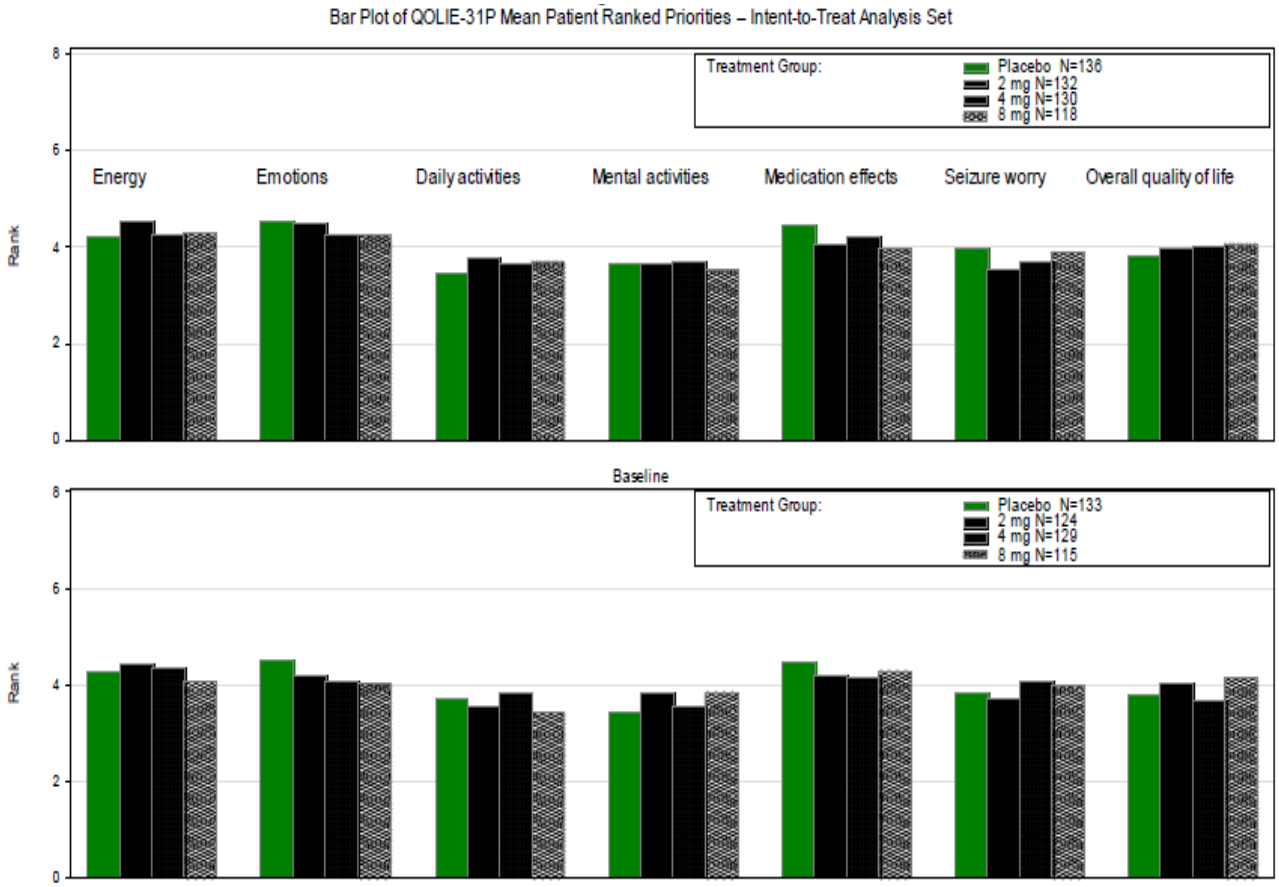


Note: 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No Change, 5=Minimally worse, 6=Much worse, 7=Very much worse.

QOLIE-31-P

The QOLIE-31-P results for the ITT Analysis Set including: change from baseline to end of treatment, percent change from baseline to end of treatment and percentages of subjects with ≥ 12-point improvement (i.e., clinically meaningful improvement) in the seven QOLIE-31-P subscales, plus the overall score at the end of treatment are shown in the sponsor's figure below. The changes in quality of life were similar in the placebo, 2 mg, 4 mg, and 8 mg treatment groups.

Figure 5 QOLIE-31-P Results for the ITT Analysis Set in Study 306



6.1.7 Subpopulations

Data from Studies 306, 305, and 304 were pooled for additional analyses of efficacy in various subpopulations. This pooling was especially helpful for perampanel doses of 8 mg and 12 mg, as the 8 mg dose was evaluated in all three studies and the 12 mg dose was evaluated in two of the three studies.

The consistency of the perampanel treatment effects relative to placebo was analyzed for subgroups of subjects with different demographic backgrounds (age, sex, race, concomitant AEDs) and for subjects enrolled at US sites. The subgroup analyses for demographic background and geographic region were performed using the primary (median change in seizure frequency per 28 days during the Double-blind Phase) and secondary (responder rate and median change in frequency of complex partial plus secondarily generalized seizures per 28 days during the Double-blind Phase) efficacy variables. In addition, subgroup analyses explored the perampanel treatment effects based upon the specific concomitant AEDs being used.

Overall, the effects of perampanel, based on results of the primary and secondary efficacy variables, were consistent across all subgroups analyzed. Treatment with perampanel, at doses of 4 to 12 mg, was effective regardless of the subjects' demographic background or co-administered AEDs and for subjects enrolled at US sites.

Efficacy by Age Group

Subjects were categorized into three age subgroups: < 17 years, ≥ 17 to < 65 years, and ≥ 65 years. Of the 1478 subjects in the integrated Full ITT Analysis Set, 110 (7.4%) subjects were younger than 17 years, 1340 (90.7%) were aged from 17 years to < 65 years, and 28 (1.9%) were aged 65 years or older. The distribution of age subgroups was similar for the placebo and perampanel groups.

A summary of the results for the three efficacy variables (median percent change in seizure frequency per 28 days in the Double-blind Phase, responder rate for the Maintenance Period, median percent change in frequency of complex partial plus secondarily generalized seizures per 28 days in the Double-blind Phase) by treatment group is summarized for the age subgroups of < 17 years and ≥ 17 to < 65 years (integrated Full ITT Analysis Set) in the sponsor's table below. Because of the small number of subjects aged ≥ 65 years, differences among the treatment groups for this age subgroup would not allow a meaningful evaluation.

Results for the < 17 years of age subgroup analyses indicated that perampanel at doses of 4 mg to 12 mg was effective relative to placebo in reducing the frequency of all partial-onset seizures as well as complex partial plus secondarily

generalized seizures, during the Double-blind Phase relative to Prerandomization. Additionally, treatment with perampanel doses of 4 mg to 12 mg resulted in higher responder rates during the Maintenance Period (when doses were more stable). The magnitude of the treatment effect (median difference relative to placebo) for the median percent change in seizure frequency per 28 days for perampanel doses of 4, 8, and 12 mg was similar among the < 17 and 17 to < 65 year-old subgroups.

Table 24 Summary of Efficacy Variables by Age Group

Subgroup		Perampanel			
Parameter/Statistics	Placebo	2 mg	4 mg	8 mg	12 mg
Age: < 17 years					
All partial seizure frequency per 28 days					
Total N	38	14	9	31	18
Median percent change to Double-blind Phase	-21.59	17.32	-23.91	-33.55	-40.01
Median difference to placebo (95% CI)[a]		32.60 (6.086, 58.817)	-10.19 (-41.304, 17.407)	-18.98 (-41.827, 4.491)	-23.66 (-48.172, 2.996)
Responder rate					
Total N	38	14	9	31	18
Responders, n (%)	10 (26.3)	0	2 (22.2)	12 (38.7)	9 (50.0)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	32	13	8	29	13
Median percent change to Double-blind Phase	-4.27	17.46	-40.12	-32.72	-44.59
Median difference to placebo (95% CI)[a]		27.95 (-2.723, 59.931)	-33.59 (-59.712, -6.267)	-19.15 (-49.081, 12.277)	-32.71 (-60.935, 5.243)
Age: ≥ 17 to < 65 years					
All partial seizures per 28 days					
Total N	395	163	162	391	229
Median percent change to Double-blind Phase	-12.77	-15.34	-23.41	-28.07	-26.47
Median difference to placebo (95% CI)[a]		-4.96 (-13.331, 3.161)	-12.97 (-21.326, -5.032)	-18.43 (-24.926, -12.062)	-15.48 (-22.992, -7.942)
Responder rate					
Total N	395	163	162	391	229
Responders, n (%)	73 (18.5)	34 (20.9)	47 (29.0)	138 (35.3)	77 (33.6)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	366	151	148	356	214
Median percent change to Double-blind Phase	-13.87	-22.03	-29.43	-35.65	-28.39
Median difference to placebo (95% CI)[a]		-8.18 (-17.242, 0.935)	-16.05 (-25.525, -6.442)	-21.16 (-28.288, -14.070)	-15.33 (-23.548, -6.879)

Source: Table 14.2.1.2.1; Table 14.2.2.2; Table 14.2.3.2.1.
CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy Based on Sex

The integrated Full ITT Analysis Set was comprised of 759 (51.4%) females and 719 (48.6%) males. The demographic and medical history characteristics for males and females were similar. The mean age was 34.1 and 35.5 years for males and females, respectively. The mean time since diagnosis was approximately 20 years for males and females (244.9 and 260.1 months, respectively), and about 85% of subjects in both subgroups (83.2% and 87.7%, respectively) had complex

partial with or without secondarily generalized seizures. Efficacy results for perampanel were consistent in males and females, with both subgroups showing improved seizure control with perampanel 4 mg, 8 mg, and 12 mg relative to placebo. The magnitude of the treatment effect relative to placebo for the median percent change in seizure frequency per 28 days (all partial seizures and complex partial plus secondarily generalized seizures) was higher for females than for males, as detailed in the sponsor's table.

Table 25 Treatment Effect by Sex

Subgroup		Perampanel			
Parameter/Statistics	Placebo	2 mg	4 mg	8 mg	12 mg
Sex: Males					
All partial seizure frequency per 28 days					
Total N	220	85	88	207	119
Median percent change in Double-blind Phase	-15.00	-16.33	-17.91	-22.82	-24.84
Median difference to placebo (95% CI)[a]		-2.07 (-13.832, 9.533)	-5.87 (-16.695, 5.065)	-11.48 (-20.045, -2.538)	-11.76 (-22.451, -0.971)
Responder rate					
Total n	220	85	88	207	119
Responders, n (%)	38 (17.3)	20 (23.5)	23 (26.1)	64 (30.9)	40 (33.6)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	203	78	79	185	107
Median percent change in Double-blind Phase	-16.42	-13.47	-30.53	-31.67	-22.93
Median difference to placebo (95% CI)[a]		0.48 (-12.171, 12.628)	-9.81 (-22.484, 3.643)	-13.78 (-23.311, -3.630)	-8.80 (-20.603, 3.250)
Sex: Females					
All partial seizures per 28 days					
Total N	221	95	84	224	135
Median percent change in Double-blind Phase	-11.61	-12.20	-26.19	-34.15	-30.16
Median difference to placebo (95% CI)[a]		-3.54 (-14.633, 7.219)	-18.94 (-30.126, -7.843)	-23.99 (-32.732, -15.614)	-19.61 (-29.371, -9.484)
Responder rate					
Total N	221	95	84	224	135
Responders, n (%)	47 (21.3)	17 (17.9)	26 (31.0)	88 (39.3)	49 (36.3)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	202	89	78	208	126
Median percent change in Double-blind Phase	-12.35	-25.07	-32.31	-39.54	-33.45
Median difference to placebo (95% CI)[a]		-11.39 (-23.901, 0.514)	-24.72 (-35.932, -8.957)	-27.72 (-37.296, -17.948)	-22.67 (-33.407, -11.799)

Source: Table 14.2.1.4.1; Table 14.2.2.4; Table 14.2.3.4.1.
CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy Based on Race

About three-quarters of the 1478 subjects in the integrated Full ITT Analysis Set were White. The distribution of the remaining subjects was 19.6% Asian or Pacific Islander, 2.1%, Black or African American, and 3.0% of other racial origins. The distribution of racial subgroups was similar for the placebo and perampanel groups. In all racial subgroups, a complex partial plus secondarily generalized seizure was the most common seizure type at baseline. The percentage of female subjects was higher for the Black/African American subgroup (64.5%) than for the other three racial subgroups, and the mean time since epilepsy diagnosis was shorter for the Asian or Pacific Islander subgroup than for the other three racial subgroups.

Because of the very small number of subjects in the Black/African American or other racial subgroups, the principal subgroup analyses of efficacy based on race compare Whites and Asian or Pacific Islanders. A summary of the results for the three efficacy variables by treatment group is summarized for the racial subgroups of White and Asian or Pacific Islander (pooled Full ITT Analysis Set) is detailed in the sponsor's table below.

Table 26 Summary of efficacy variable by race

Subgroup Parameter/Statistics		Perampanel			
	Placebo	2 mg	4 mg	8 mg	12 mg
Race: White					
All partial seizure frequency per 28 days					
Total N	337	119	105	338	215
Median percent change in Double-blind Phase	-12.77	-10.71	-23.91	-25.87	-25.77
Median difference to placebo (95% CI)[a]		0.05 (-9.565, 9.583)	-15.76 (-25.337, -5.920)	-15.53 (-22.394, -8.634)	-14.75 (-22.665, -7.009)
Responder rate					
Total N	337	119	105	338	215
Responders, n (%)	63 (18.7)	24 (20.2)	34 (32.4)	110 (32.5)	69 (32.1)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	310	112	100	309	199
Median percent change in Double-blind Phase	-13.08	-12.53	-35.61	-32.72	-28.41
Median difference to placebo (95% CI)[a]		-3.38 (-13.862, 7.260)	-19.38 (-29.659, -8.179)	-18.80 (-26.565, -11.038)	-15.75 (-24.563, -6.850)
Race: Asian or Pacific Islander					
All partial seizures per 28 days					
Total N	76	60	66	69	18
Median percent change in Double-blind Phase	-11.57	-19.78	-22.04	-39.29	-33.82
Median difference to placebo (95% CI)[a]		-6.86 (-22.053, 7.786)	-4.95 (-20.769, 9.972)	-26.19 (-41.473, -10.814)	-15.49 (-39.780, 14.635)
Responder rate					
Total N	76	60	66	69	18
Responders, n (%)	16 (21.1)	13 (21.7)	15 (22.7)	33 (47.8)	9 (50.0)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	68	54	56	62	15
Median percent change in Double-blind Phase	-19.18	-26.59	-28.87	-47.20	-11.54
Median difference to placebo (95% CI)[a]		-8.78 (-25.437, 7.352)	-9.38 (-28.709, 7.866)	-26.33 (-42.840, -9.225)	-7.54 (-36.970, 28.901)

Source: Table 14.2.1.3.1; Table 14.2.2.3; Table 14.2.3.3.1.
CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Improvements in seizure control were seen for perampanel compared to placebo in both racial subgroups. The efficacy for the White subgroup was consistent with that described for the overall study population. (This would be expected since this race comprised about three-quarters of all subjects in the integrated Full ITT Analysis Set.) For the Asian or Pacific Islander subgroup, reductions in seizure frequency per 28 days during the Double-blind Phase, as well as the proportion of subjects achieving at least a 50% reduction in seizure frequency during the Maintenance Period, were consistently larger for the perampanel 8-mg and 12-mg groups than for the placebo group.

Among the Asian and Pacific Islander subgroup, the magnitude of the treatment effect relative to placebo for median changes in seizure frequency was less in the perampanel 2-mg and 4-mg groups, and the responder rates for perampanel 2 mg and 4 mg were similar to those for placebo.

There were fewer than 10 Black/African American subjects within each treatment group (none in the 2 mg or 4 mg groups). It is not possible to meaningfully evaluate differences among the treatment groups for these racial subgroups. (For this reason, data for these two subgroups are not included in the table.) There was no indication that the pattern of efficacy for perampanel (4 mg to 12 mg) compared with placebo differed in the Black/African American or other racial subgroups relative to the larger racial subgroups or to the overall population.

Effect of Concomitant AEDs

The results of the population PK analysis indicated a two- to three-fold increase in the clearance of perampanel in both male and female subjects receiving co-administered carbamazepine (three-fold increase), oxcarbazepine (two-fold increase), or phenytoin (two-fold increase). The therapeutic effects of perampanel were examined for subgroups treated concomitantly with at least one of the three inducer AEDs (perampanel inducer subgroups) compared to the subgroup whose background AED therapy did not include one of these AEDs (perampanel noninducer subgroup).

Using data from Studies 305 and 304 to further assess the effects at 8 mg and 12 mg, the median treatment difference versus placebo in the percent change in seizure frequency per 28 days in the Maintenance Period among subjects in the perampanel noninducer AED subgroup was similar to that for subjects receiving concomitant therapy with carbamazepine or oxcarbazepine at the 8 mg perampanel dose, higher in subjects receiving the 12 mg dose. Higher responder rates during the Maintenance Period for perampanel 8 mg and 12 mg compared

with placebo were seen regardless of perampanel AED inducer use. The response rate during the Maintenance Period was higher for subjects on adjunctive perampanel 8 mg or 12 mg therapy in the perampanel noninducer AED subgroup compared to subjects in either of the two perampanel AED inducer subgroups. These results suggest that the induction effects of carbamazepine and oxcarbazepine on perampanel clearance have a small effect on perampanel response at these higher doses. The explanation for this observation remains unclear.

Results were similar for Study 306. The median percent reductions in seizure frequency per 28 days in the Maintenance Period were larger, and the responder rates were higher, for perampanel doses of 4 and 8 mg compared with placebo or perampanel 2 mg for subjects receiving concomitant therapy with perampanel AED inducers than those not on a co-administered perampanel AED inducer. Once again, the explanation for this clinical vs. PK discrepancy remains unclear.

The sponsor's table below shows the median percent change in seizure frequency and responder rate during the maintenance period by last dose and baseline co-administered AEDs, completer analysis set for Studies 305 and 304, excluding central and South American sites.

Table 27 Effect of Concomitant AEDs on Efficacy in Studies 305 and 304

Parameter/ Statistics	Concomitant CBZ, OXC, PHY			Concomitant CBZ or OXC			No Concomitant CBZ, OXC, or PHY		
		Perampanel Last Dose			Perampanel Last Dose			Perampanel Last Dose	
	Placebo	8 mg	12 mg	Placebo	8 mg	12 mg	Placebo	8 mg	12 mg
All partial seizure frequency per 28 days									
Total N	102	94	79	91	77	67	80	64	35
Median frequency – Prerandomization	14.74	10.21	12.78	12.98	10.50	13.66	10.72	13.84	17.18
Median percent change in Maintenance Period	-8.68	-25.82	-22.62	-5.87	-32.37	-27.82	-19.96	-50.63	-54.17
Median difference to placebo (95% CI)[a]		-17.77 (-31.807, -3.872)	-19.21 (-34.269, -4.409)		-25.92 (-40.446, -11.170)	-26.92 (-42.396, -11.338)		-24.37 (-37.818, -10.163)	-33.22 (-47.253, -17.673)
Responder rate									
Total N	102	94	79	91	77	67	80	64	35
Responders, n (%)	21 (20	29 (30.9)	26 (32.9)	17 (18	27 (35.1)	24 (35.8)	12 (15	32 (50.0)	19 (54.3)

Source: 5.3.5.3, Table 14.2.6.6; 5.3.5.3, Table 14.2.6.7.
AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.
Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

The sponsor's table below shows the median percent change in seizure frequency and responder rate during maintenance period by last (actual) dose and baseline co-administered AED, Completer Analysis set for Study 306.

Table 28 Effect of Concomitant AEDs on Efficacy in Study 306

Statistics	All Partial Seizure Frequency per 28 days				Responder Rate	
	Total N	Median Prerandomization frequency	Median % change in Maintenance Period	Median difference to placebo (95% CI)[a]	Total N	Responder, n (%)
Concomitant CBZ, OXC, PHY						
Placebo	94	11.27	-14.39	--	94	17 (18.1)
Perampanel 2 mg	90	10.71	-16.40	-0.46 (-14.255, 12.712)	90	18 (20.0)
Perampanel 4 mg	84	11.33	-32.66	-11.86 (-24.469, 1.607)	84	22 (26.2)
Perampanel 8 mg	76	8.88	-22.92	-10.82 (-26.083, 4.654)	76	26 (34.2)
Concomitant CBZ or OXC						
Placebo	88	10.59	-13.93	--	88	15 (17.0)
Perampanel 2 mg	80	10.71	-14.44	-0.19 (-14.985, 13.534)	80	15 (18.8)
Perampanel 4 mg	72	11.19	-32.66	-13.46 (-26.396, 0.250)	72	19 (26.4)
Perampanel 8 mg	71	8.88	-24.34	-11.89 (-27.582, 3.806)	71	24 (33.8)
No concomitant CBZ, OXC, PHY						
Placebo	72	8.23	-16.04	--	72	14 (19.4)
Perampanel 2 mg	70	8.88	-22.81	-8.15 (-24.315, 7.057)	70	18 (25.7)
Perampanel 4 mg	69	9.56	-21.90	-15.31 (-31.125, 1.334)	69	24 (34.8)
Perampanel 8 mg	53	11.61	-40.27	-27.60 (-44.872, -11.385)	53	21 (39.6)

Source: 5.3.5.3, Table 14.2.6.9; 5.3.5.3, Table 14.2.6.10; 5.3.5.3, Table 14.2.6.11; 5.3.5.3, Table 14.2.6.12.
AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.
Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy at US Sites

Of the 1478 subjects in the integrated Full ITT Analysis Set, 293 (19.8%) were enrolled at sites in the US. These subjects came from Study 304 and Study 305; no US sites were involved in Study 306. For this reason, there are no data for perampanel doses of 2 mg and 4 mg in the US subgroup.

The US subjects in the integrated Full ITT Analysis Set had a mean age of 36.8 years and were predominately White (80.2%); 48.8% of subjects were male and 51.2% were female. The mean time since diagnosis was approximately 24 years and 89.1% of subjects had complex partial with or without secondarily generalized seizures. Approximately one-third of US subjects were receiving background therapy with three AEDs (32.1%), and 53.9% were receiving concomitant therapy with two AEDs. This pattern of demographic and epilepsy-specific characteristics was consistent with that of all subjects in the Full ITT Analysis Set for the Phase 3 studies.

Improved seizure control was demonstrated for adjunctive therapy with perampanel 8 mg and 12 mg among US subjects having partial-onset seizures, as detailed in the sponsor's table below.

Table 29 Seizure Control in US sites

Parameter/Statistics	Placebo	Perampanel 8 mg	Perampanel 12 mg
All partial seizure frequency per 28 days			
Total N	99	95	99
Median percent change in Double-blind Phase	-15.90	-32.72	-33.86
Median difference to placebo (95% CI)[a]		-22.26 (-35.303, -9.413)	-20.81 (-33.766, -8.767)
Responder rate			
Total N	99	95	99
Responders, n (%)	17 (17.2)	38 (40.0)	42 (42.4)
Complex partial plus secondarily generalized seizures per 28 days			
Total N	90	92	90
Median percent change in Double-blind Phase	-16.16	-39.92	-34.90
Median difference to placebo (95% CI)[a]		-26.03 (-39.138, -12.783)	-21.00 (-34.393, -8.179)

Source: Table 14.2.1.5.1; Table 14.2.2.5; Table 14.2.3.5.1.
CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

The magnitude of the treatment differences relative to placebo for the median percent changes in all partial-onset seizures as well as for complex partial plus secondarily generalized seizures for the US subgroup was numerically greater than the corresponding values for the 8 mg and 12 mg perampanel groups for the entire integrated Full ITT Analysis Set. The same was true for the magnitude of the responder rate for the US subgroup compared with the entire integrated Full ITT Analysis Set. To further assess this, data from all regions across the three Phase 3 studies, data from the common treatment groups of placebo and 8 mg in Studies 304, 305 and 306 were pooled. A rank ANCOVA was used to analyze the percent change from baseline per 28 days during the treatment period for the Full ITT analysis set. The ANCOVA included the rank-transformed percent change from baseline as the dependent variable, rank-transformed baseline seizure frequency as a covariate, and treatment, region, and treatment-by-region as factors.

These results are displayed in the sponsor's table below as the percent change in seizure frequency per 28 days during the double-blind phase relative to prerandomization for subjects who received placebo or 8mg perampanel (Studies 306, 305 and 304) by region (Full Intent-to-Treat Analysis Set).

Table 30 Percent Change in Seizure Frequency by Region

Region/Statistics	Placebo	8 mg Perampanel
North America		
N	106	105
Mean	1.65 (77.898)	-31.86 (44.521)
Median	-16.16	-34.20
Min, Max	-100.0, 404.3	-100.0, 103.1
Median Difference to Placebo		-23.74
(95% Confidence Interval)[a]		(-36.364,-10.879)
Central and South America		
N	48	59
Mean	-26.92 (35.932)	-17.42 (52.707)
Median	-26.18	-24.88
Min, Max	-88.8, 111.5	-95.6, 150.7
Median Difference to Placebo		5.02
(95% Confidence Interval)[a]		(-11.263, 24.568)
Europe		
N	192	181
Mean	7.07 (71.840)	-14.90 (61.780)
Median	-7.13	-23.25
Min, Max	-95.5, 420.6	-100.0, 390.6
Median Difference to Placebo		-19.26
(95% Confidence Interval)[a]		(-28.869,-10.097)
Asia Pacific		
N	74	65
Mean	-6.05 (51.131)	-29.24 (45.858)
Median	-11.57	-38.89
Min, Max	-100.0, 192.9	-93.9, 127.3
Median Difference to Placebo		-22.83
(95% Confidence Interval)[a]		(-37.687, -6.533)

Among US sites, the treatment differences relative to placebo in the median percent change in seizure frequency per 28 days during the Double-blind Phase were -28.06% for the 8 mg group and –31.25% for the 12 mg group; the P values associated with these treatment differences were 0.0020 and 0.0002, respectively (rank ANCOVA). Among US sites, the responder rates during the Maintenance Period (with LOCF imputation) were 37.5% and 43.1% for the 8 mg and 12 mg groups, compared with 16.7% for the placebo group; the P values for the differences to placebo were 0.0077 for 8 mg and 0.0008 for 12 mg . Among US sites, the treatment differences relative to placebo in the median percent change in the frequency of complex partial plus secondarily generalized seizures per 28 days during the Double-blind Phase were -31.5% for the 8 mg group and -31.17% for the 12 mg group; the P values associated with these treatment differences were 0.0002 and 0.0002, respectively (rank ANCOVA). Results of subgroup

analyses based on region for sites in North America were consistent with those for the US subgroup (202 of 227 subjects in North America were from US).

In the subgroup from Central and South America, there was no difference between either perampanel group and the placebo group in the median percent change in seizure frequency per 28 days during the Double-blind Phase (P = 0.5121 for the 8 mg group; P = 0.5151 for the 12 mg group) or in the responder rate during the Maintenance Period (P = 0.9335 for the 8 mg group; P = 0.7925 for the 12 mg group).

The lack of efficacy observed for perampanel in the Central and South American subgroup in Study 304 appears to be related to the high response to placebo in this regional subgroup. In the placebo group for the Central and South American subgroup, the median percent change in seizure frequency during Double-blind Phase was -26.18%, and the responder rate was 33.3%. Corresponding figures for the placebo group in the North American subgroup were -11.34% and 21.9%, respectively. The median change in seizure frequency per 28 days during the Double-blind Phase for the placebo group in the US subgroup (or North American subgroup) was consistent with results seen for placebo in Studies 306 and 305. The dose-response analysis focused on the Maintenance Period (Full ITT Analysis Set, LOCF) when the doses of perampanel became more stable. The median percent change in the frequency of all partial seizures was greater in the 12 mg group (-34.49%) than in the 8 mg group (–26.34%).

The sponsor attempted to explain the high placebo rate in Central and South America by performing multiple analyses. These explorations include evaluating the influence of demographic and baseline characteristics (age and baseline body weight) and concomitant AEDs on the efficacy results for the Central and South American region. For these analyses, data from the integrated Phase 3 Full ITT Analysis Set were used; in this integrated analysis set, only subjects from Study 304 contributed to the Central and South American regional subgroup.

The mean age for subjects in Central and South America (34.7 years) was younger than that for subjects in North America (36.6 years), and there were fewer adolescent subjects (<18 years) enrolled in sites in Central and South America (6.9% vs. 15.1% for North America). It is unlikely, however, that this age difference contributed to the high placebo response in Central and South America for Study 304, as subjects enrolled at sites in Asia-Pacific study sites were also younger (mean age of 31.1 years) and had fewer adolescents (4.0%) compared to subjects enrolled at North American sites. There was no indication of a greater placebo response among Asia-Pacific subjects.

The mean body weight and body mass index (BMI) was lower for Central and South American subjects (67.36 kg and 25.21 kg/m2, respectively) compared to North American subjects (75.64 kg and 26.90 kg/m2, respectively). Again, the mean body weight and BMI values for Central and South American subjects was comparable to those for Asian-Pacific subjects (60.13 kg and 22.54 kg/m2), and it therefore seems unlikely that a difference in these parameters contributed to the high placebo response in Central and South America for Study 304. The individual AEDs at baseline were similar across regions both for the relative incidence of individual AEDs as well as for the incidence of use of carbamazepine, oxcarbazepine, and phenytoin (perampanel inducers) The use of concomitant non-AED medication also showed no notable differences among regions. In this reviewer's opinion, no reasonable explanation has been proposed which might explain this high placebo rate in Central and South America.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The time to the onset of activity for perampanel, up to the minimum effective dose of 4 mg, was explored in analyses of the percent change in seizure frequency relative to the Prerandomization Phase during the first 2 weeks of the Titration Period for the Full ITT Analysis Set based on integrated data from Studies 306, 305, and 304. As designated in the Protocol, all subjects randomized to perampanel received a daily dose of 2 mg during Week 1 of the Titration Period, and subjects randomized to the perampanel 4 mg, 8 mg, or 12 mg groups received a daily dose of 4 mg during Week 2 of the Titration Period.
The minimally effective dose for perampanel as adjunctive therapy in partial-onset seizures in Study 306 appears to be 4 mg. Thus, the onset of clinically meaningful seizure improvement with perampanel seems to appear as early as the second week of treatment if the subject is titrated at a rate increase of 2 mg/week. This observation is consistent with PK simulations based on plasma concentration data obtained from healthy subjects which showed that, for the 4 mg perampanel dose (with titration), about 85% of average steady-state perampanel concentration is achieved at the start of the second week of treatment, and 97% of the average perampanel concentration is achieved at the start of the third week of 4 mg/day treatment.

A once daily dose regimen was established by Phase 2 Study 206 where subjects who were randomly assigned to adjunctive perampanel treatment were titrated over the dose range of 1 mg to 4 mg, and perampanel was administered either once or twice daily. Results were similar for the QD and BID perampanel groups. Based on this finding, the once-daily dosing regimen was used in all subsequent

clinical studies of perampanel in partial-onset seizures. In the Phase 3 studies, perampanel was administered with food at bedtime. Administration with food is supported by results of Phase 1 studies which showed that dosing with food slowed drug absorption without changing the extent of absorption. Dosing before bedtime was selected to minimize sedation and/or somnolence. Once-daily dosing of perampanel is further supported based on its half-life, which averages more than 72 hours in healthy subjects not receiving a perampanel AED inducer, and still more than 24 hours in healthy subjects receiving carbamazepine.

Because of perampanel's long half life, a 2-week interval (the time likely needed to reach steady state) between doses was evaluated in Phase 2 Studies 206 and 208. Although steady states may not have been completely reached in less than two weeks, weekly titration was chosen because of the good tolerability shown for perampanel at doses up to 12 mg/day in these studies. In the Phase 3 studies, perampanel treatment was initiated at a dose of 2 mg/day and doses were adjusted upward in 2 mg increments on a weekly basis to the randomly assigned dose.

Due to its half-life of 70 to 110 hours, none of the clinical studies with perampanel included a down-titration schedule. There was no increased seizure activity following discontinuation of perampanel doses of 2 mg to 12 mg in the Phase 3 studies and no adverse event reports.

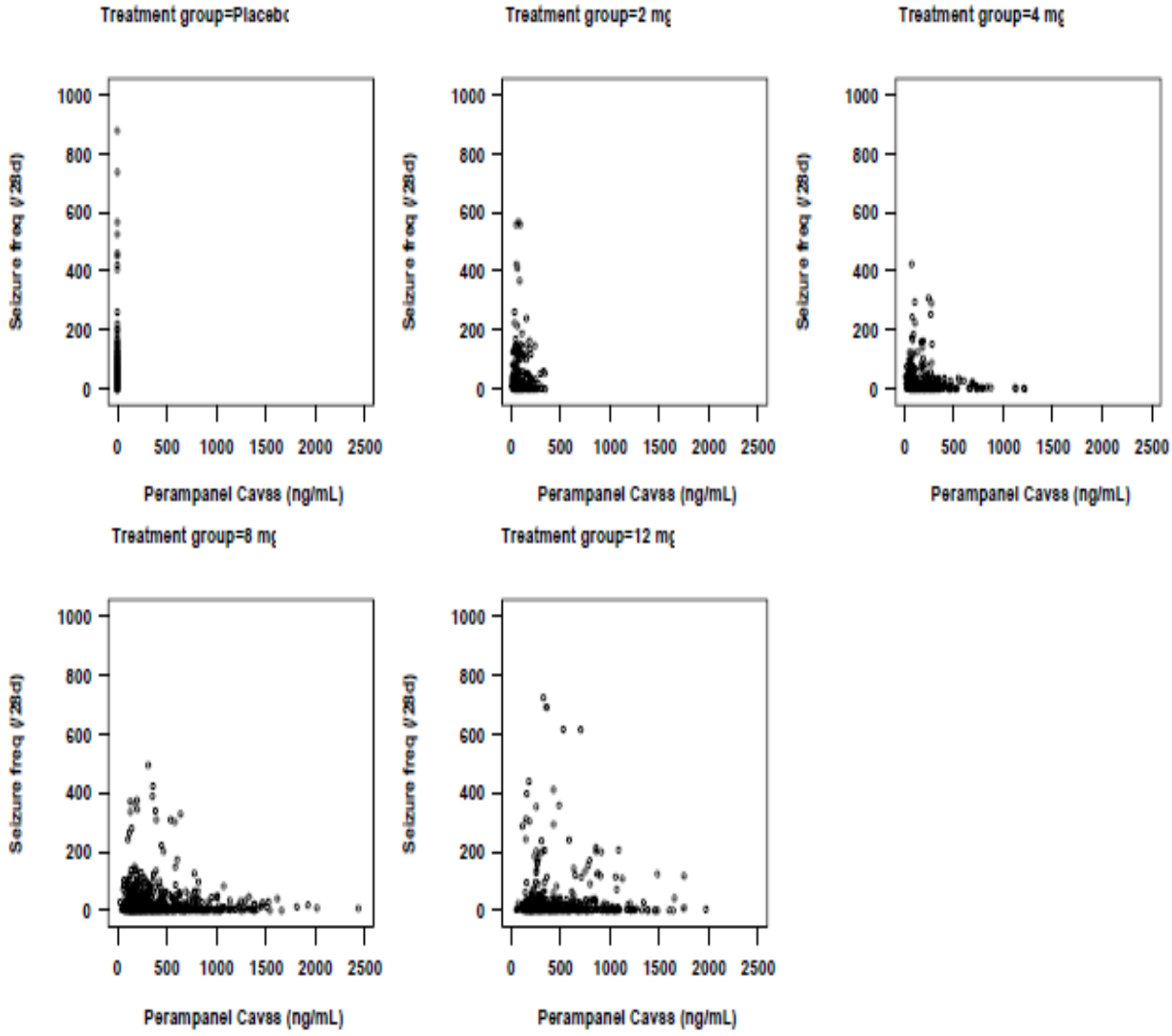
The selection of the dosage range evaluated in the Phase 3 studies was based on data gathered from Phase 2 studies. In Study 208, subjects randomly assigned to adjunctive perampanel treatment were titrated to their MTD over the dose range of 2 mg to 12 mg. Results from this study, together with those from Study 206, showed benefit and tolerability across the dose range tested. Results of the PK/PD analysis of these Phase 2 studies were used to select the doses to evaluate in the Phase 3 studies (no effect = 2 mg, minimum effective dose = 4 mg, mid-range effective dose = 8 mg, and high effective dose = 12 mg).

Results of the population PK analysis for the Phase 3 studies showed that exposure to perampanel increased approximately proportionally with doses between 2 and 12 mg. The geometric mean concentrations of perampanel were 71, 138, 272, and 349 ng/mL for the perampanel dose groups of 2 mg, 4 mg, 8 mg and 12 mg, respectively.

The relationship between plasma concentration of perampanel and anti-seizure effects was explored in the population PK/PD analysis using data from the Phase 3 studies. There was an inverse relationship between steady-state perampanel plasma concentration and seizure frequency. The slope for the relationship between seizure frequency and plasma concentrations associated with doses of 8 to 12 mg was not significantly different from the slope for the relationship

between seizure frequency and concentrations associated with doses of 4 to 8 mg. The sponsor's figure below shows the total seizure frequency as a function of perampanel concentration.

Figure 6 Total seizure frequency as a function of perampanel concentration



Analyses of the percent change in seizure frequency per 28 days relative to the Prerandomizaton Phase and responder rate using the integrated Full ITT Analysis Set for the Phase 3 studies were performed based on each randomized dose group. These analyses were limited to the Maintenance Period (with LOCF imputation) where doses of perampanel were more stable. The lowest perampanel dose of 2 mg did not provide any benefit in terms of improved seizure control compared with placebo. Once daily perampanel doses of 8 mg and 12 mg produced greater reductions in seizure frequency and improved responder rates compared with the once daily dose of 4 mg. However, in these analyses there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose. The median differences versus placebo in change in seizure frequency during the Maintenance Period for the 8 and 12 mg groups were –16.43% and -15.79%, respectively, while the responder rates were 35.3% and 35.0%, respectively. These results were consistent with results for Study 305 and to a lesser extent for Study 304, when analyzed individually.

Additional analyses were performed on the percent change in seizure frequency and responder rate during the Maintenance Period in each randomized dose group using the integrated Full ITT Analysis Set, but excluding subjects from sites in Central and South America where there was an unusual outcome, perhaps due to the high placebo response rate. Results of these analyses were consistent in showing better efficacy for the 8 and 12 mg dose groups than for the 4 mg dose group, but no clear separation between these two highest randomized perampanel dose groups.

In order to further compare the potential benefit of 12mg over 8mg of perampanel daily, the sponsor attempted to see if there was an incremental benefit associated with the 12-mg dose of perampanel relative to the 8-mg dose in individual patients. This was an attempt to examine efficacy responses in subjects who received treatment with both doses, rather than comparing separate groups of subjects. Subjects who completed a double-blind Phase 3 study were enrolled into the long-term OLE study (Study 307) and underwent blinded titration to a maximum dose of 12 mg/day. Thus, data from controlled Phase 3 studies, coupled with those from the blinded Conversion Period (16 weeks), permitted an investigation of effectiveness in the same subject in both doses of 8 and 12 mg.

The results were consistent in showing better efficacy in the same subjects when the dose of perampanel was increased from 8 mg to 12 mg. Of particular note, seizure frequency decreased further from −32.42% at the double-blind Maintenance Period to −43.27% at the blinded Conversion Period, and the 50% responder rate rose from 37.8% on a dose of 8 mg in the double-blind Maintenance Period to 43.5% in the same subjects on a dose of 12 mg in the

blinded Conversion Period. It therefore appears that some patients might benefit from perampanel 12 mg, if the associated adverse side-effects could be tolerated.

The change in seizure frequency per 28 days and responder rate for subjects who were randomized to and completed the double-blind Maintenance Period (Studies 304, 305, and 306) on 8 mg and received 12 mg as their last dose in the blinded conversion period (Study 307) (Full ITT Analysis Set) are shown in the sponsor's table below.

Table 31 Change in Seizure Frequency and Responder Rate in those on 8 mg Blindly Converted to 12 mg

Parameter	DB Actual Dose → Conversion Period Actual Dose
Statistic/ Timepoint	8 mg → 12 mg
Seizure frequency per 28 days	
N	209
Median Prerandomization	10.50
Median percent change from Prerandomization	
DB Maintenance Period	−32.42
Blinded Conversion Period (Study 307, Weeks 1-16)	−43.27
Responder rate	
Response, n (%)	
DB Maintenance Period	79 (37.8)
Blinded Conversion Period (Study 307, Weeks 1-16)	91 (43.5)

Source: Table 14.2.7.4.1; Table 14.2.7.5.1
DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension.
Note: Only subjects who had valid seizure data in the blinded Conversion Period in Study 307 are presented. Data exclude Central and South America sites.

The results were very similar in showing incremental benefit when the perampanel dose was increased from 8 mg in the double-blind Maintenance Period compared to 12 mg in Weeks 1-13 of the OLE Maintenance Period. The sponsor's table below shows the change in seizure frequency and responder rate for subjects who were randomized to and completed the double-blind maintenance period (Studies 304, 305 and 306) on 8 mg and received 12 mg as

their last dose in the open-label maintenance period Study 307 (Full ITT Analysis Set).

Table 32 Change in Seizure Frequency and Responder Rate from those on 8 mg in Maintenance Period to 12 mg in the OLE Maintenance Period

Parameter Statistic/ Timepoint	DB Actual Dose → OLE Actual Dose
	8 mg → 12 mg
Seizure frequency per 28 days	
N	143
Median Prerandomization	9.77
Median percent change from Prerandomization	
DB Maintenance Period	-31.67
OLE Maintenance Week 1-13	-49.31
Responder rate, n (%)	
N	143
DB Maintenance Period	55 (38.5)
OLE Maintenance Week 1-13	69 (48.3)

Source: Table 14.2.7.1.1; Table 14.2.7.2.1.
DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension study.
Note: Only subjects who had valid seizure data in OLE Maintenance Weeks 1-13 are presented.

Seizure-free status for subjects who were randomized to and completed the double-blind Maintenance Period at a dose of 8 mg perampanel and completed Weeks 1-13 of the open-label Maintenance Period (Study 307) on 12 mg were analyzed. Seizure-free status among subjects who completed both Maintenance Periods increased from 5.4% (during the double-blind Maintenance Period) to 15.5% (during the open-label Maintenance Period Weeks 1-13). Similarly, in subjects who completed both Maintenance Periods and who were titrated from 8 mg to 12 mg, there was an increase in the proportion that were seizure-free during the last 28 days from 13.2% (double-blind Maintenance Period) to 20.9% (open-label Maintenance Period Weeks 1-13). There was also an increase in the proportion of subjects who were seizure-free among subjects who had a last dose of 12 mg perampanel in both the double-blind and open-label Maintenance Periods.

The number of seizure free days for subjects who were randomized to and completed the double-blind maintenance period (Studies 304, 305, and 306) on 8

mg and completed week 1-13 of the open-label maintenance period (Study 307) on 12 mg (Full ITT analysis Set) are shown in the sponsor's table below.

Table 33 Seizure Free Days for those on 8 mg in Maintenance Period to 12 mg in the OLE Maintenance Period

	DB Actual Dose → OLE Actual Dose
Statistic/ Timepoint	8 mg → 12 mg
Subjects who completed both Maintenance Periods	
N	129
Seizure-free, n (%)	
During the entire DB Maintenance Period	7 (5.4)
During the entire OLE Maintenance Weeks 1-13	20 (15.5)
During the last 28 Days of DB Maintenance Period	17 (13.2)
During the last 28 Days of OLE Maintenance Weeks 1-13	27 (20.9)

Source: Table 14.2.7.3.1
DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension study.

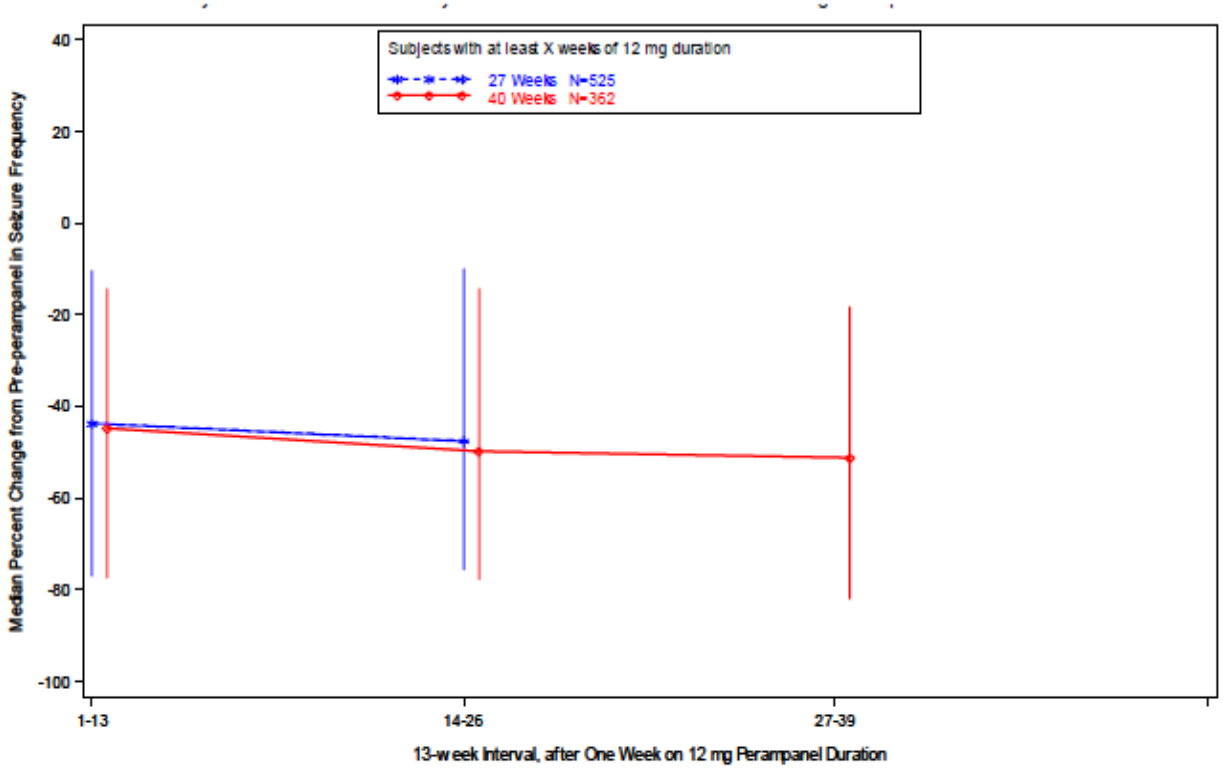
Therefore, even though there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose in the Phase 3 efficacy studies, there does appear to be an incremental benefit associated with the 12-mg dose of perampanel relative to the 8-mg dose in individual patients who received treatment with both doses. Once again, the 12 mg dose was associated with a greater number of AEs, many of which could not be tolerated.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Results relevant to the safety of long-term treatment with perampanel come from the three ongoing OLE studies (Studies 307, 207, and 233). A total of 703 subjects in those studies have received perampanel for at least 1 year and 95 have received perampanel for at least 2 years (combined exposure to double-blind and open-label perampanel). Some subjects have been treated for as long as 3 years (n=57) or 4 years (n=26). Among these subjects, no new safety signals were seen during long-term treatment with perampanel and, according to the sponsor, there was no clinically notable worsening in the frequencies of safety findings.

The data from the OLE studies show sustained improvement in seizure control for subjects who remained on the same efficacious dose of perampanel for up to approximately 9 months. There was no decrement in efficacy over this period. The sponsor's figure below shows the median percent change from pre-perampanel baseline in seizure frequency per 28 days, by 13-week intervals, after one week on 12 mg perampanel, full ITT Analysis Set for Study 307 with at least 27 or 40 weeks of 12-mg perampanel treatment duration.

Figure 7 Maintenance of Seizure Control with a Fixed Dose of Perampanel



A vertical line denotes the 3rd quartile to the 1st quartile, and a symbol in the vertical line stands for the median percent change. The X weeks of 12 mg perampanel duration starts on the first day of 12 mg and ends X weeks later on 12 mg. The 13-week intervals start one week after starting 12 mg. For example, Weeks 1-13 is the first 13-week interval, one week after starting 12 mg.

6.1.10 Summation of Efficacy Analyses of Primary and Secondary Endpoints

The following is a summary tabulation of the key efficacy results (primary and secondary) for each of the three adequate and well controlled Phase 3 clinical trials analyzed in order to render an opinion on the efficacy of perampanel as adjunctive treatment partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Once-daily administration of perampanel doses of 4 mg, 8 mg, and 12 mg appears to have significantly improved seizure control in these subjects when compared to placebo, as shown by larger reductions in the frequency of partial-onset seizures and complex partial plus secondarily generalized seizures and greater responder rates.

Study 306

Results for the primary and secondary efficacy variables in Study 306 were examined for subgroups for different countries. Although the number of subjects was small for several countries, results were consistent across countries in showing greater improvements in seizure control for perampanel compared with placebo. No US sites were included in this study. The following sponsor's table shows an overview of key primary and secondary results for the full ITT analysis set for Study 306.

Table 34 An overview of key primary and secondary results for the full ITT analysis set for Study 306

Parameter Statistic	Placebo (N=184)	Perampanel 2 mg/d (N=180)	Perampanel 4 mg/d (N=172)	Perampanel 8 mg/d (N=169)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization				
N		180	172	169
Median change	-10.69	-13.63	-23.33	-30.80
Median difference from placebo (95% CI)[a]		-4.36 (-14.091, 5.227)	-13.71 (-23.306, -4.500)	-20.13 (-29.656, -10.425)
P value (vs. placebo)[b]		0.4197	0.0026	<0.0001
Responder Rate during Maintenance-LOCF Period				
N		180	172	169
Number (%) responders[c]	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
P value (vs.placebo)[d]		0.4863	0.0132	0.0003
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization				
N		167	157	154
Median change	-17.63	-20.50	-31.18	-38.69
Median difference from placebo (95% CI)[a]		-3.26 (-13.685, 7.395)	-14.40 (-25.082, -3.496)	-19.32 (-29.788, -8.625)
P value (vs placebo)[b]		0.6506	0.0070	0.0005

Source: 306, Table 14.2.1.1.6.1; 306, Table 14.2.2.3.5; 306, Table 14.2.10.1.
ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.
c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.
d: The *P* value is based on non-missing values and is from the CMH test adjusted for pooled country.

Study 305

Results for the primary and secondary efficacy variables in Study 305 were examined, and are shown for the Full ITT Analysis Set in the sponsor's table below. Although the number of subjects was small for several countries, the results were consistent across countries in showing greater improvements in seizure control for perampanel compared with placebo. Approximately 25%of subjects in this study were enrolled at sites in the US. In the pooled US subgroup, the median percent change in seizure frequency per 28 days during the Double-blind Phase was -23.31%, -41.64%, and -21.64% for the placebo, perampanel 8 mg, and perampanel 12 mg groups, respectively. The responder rates (Maintenance Period) for each treatment group were 16.1%, 45.2%, and 44.0%, respectively.

The dose-response analysis was based on the Maintenance Period (Full ITT Analysis Set) when the doses of perampanel became stable. The median percent change in the frequency of all partial seizures was greater in the 8 mg group (-32.37%) than in the 12 mg group (-24.91%).

The following sponsor's table is an overview of the key efficacy results for the full ITT analysis set in study 305.

Table 35 An overview of key primary and secondary results for the full ITT analysis set for Study 305.

Parameter Statistic	Placebo (N=136)	Perampanel 8 mg/d (N=129)	Perampanel 12 mg/d (N=121)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization			
N		129	121
Median change	-9.72	-30.52	-17.57
Median difference from placebo (95% CI)[a]		-19.10 (-29.169, -8.447)	-13.69 (-25.198, -2.257)
P value (vs placebo)[b]		0.0008	0.0105
Responder rate during Maintenance			
N		129	121
Number (%) responders[c]	20 (14.7)	43 (33.3)	41 (33.9)
P value (vs. placebo)[d]		0.0018	0.0006
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization			
N		119	113
Median change	-8.05	-32.72	-21.89
Median difference from placebo (95% CI)[a]		-23.07 (-34.798, -10.549)	-17.45 (-29.269, -5.703)
P value (vs placebo)[b]		0.0007	0.0045

Source: 305, Table 14.2.1.1.1.1; 305, Table 14.2.2.3.5.1; 305, Table 14.2.2.1.1.
ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.
c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.
d: The *P* value is based on non-missing values and is from the CMH test adjusted for pooled country.

Study 304

Results for the primary and secondary efficacy variables are detailed in the sponsor's table below. In the ITT Analysis Set, the treatment differences relative to placebo in the median percent change in seizure frequency per 28 days during the Double-blind Phase for the 8 mg (-13.17) and 12 mg (-14.47) groups were statistically significant (P = 0.0290 and P = 0.0120, respectively; rank ANCOVA). The treatment comparisons to placebo for the median percent change in seizure frequency per 28 days during the Maintenance Period (using LOCF imputation) were -11.67 for the 8 mg group (P = 0.0812) and -12.64 for the 12 mg group (P = 0.0304) (rank ANCOVA). In the ITT Analysis Set, the responder rate during the Maintenance Period (using LOCF imputation) was 26.1% in the placebo group, 37.1% in the 8 mg group (P value vs. placebo of 0.0871), and 36.2% in the 12 mg group (P value vs. placebo of 0.0776).

In Study 304, approximately half (52%) of the subjects were from sites in the US, with the remaining subjects from sites in Canada (6%) or Central and South America (42% [Chile, Argentina, Mexico]). A significant treatment-by-region difference was detected (P = 0.0035) from the analysis of the median percent change in seizure frequency per 28 days during the Maintenance Period (with LOCF imputation) using the rank ANCOVA for the ITT Analysis Set. This regional difference reflected a strong treatment effect in the North America region (mainly US), in contrast to a high placebo response and no treatment difference in the Central and South America region. Results of the primary and secondary efficacy, using the Full ITT Analysis Set for Study 304, are detailed in the sponsor's table below.

See section 6.1.7 for details.

Table 36 An overview of key primary and secondary results for the full ITT analysis set for Study 304

Parameter Statistic	Placebo (N=121)	Perampanel 8 mg/d (N=133)	Perampanel 12 mg/d (N=133)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization			
N		133	133
Median change	-20.95	-26.34	-34.49
Median difference from placebo (95% CI)[a]		-13.53 (-26.172, -1.944)	-14.20 (-25.030, -2.729)
P value (vs placebo)[b]		0.0261	0.0158
Responder Rate during Maintenance-LOCF Period			
N		133	133
Number (%) responders[c]	32 (26.4)	50 (37.6)	48 (36.1)
P value (vs.placebo)[d]		0.0760	0.0914
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization			
N		120	120
Median change	-17.88	-33.03	-33.06
Median difference from placebo (95% CI)[a]		-20.37 (-33.164, -7.741)	-17.90 (-30.313, -4.665)
P value (vs placebo)[b]		0.0020	0.0081

Source: 304, Table 14.2.1.1.6.1; 304, Table 14.2.2.3.5.1; 304, Table 14.2.14.1.1
ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.
c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.
d: The *P* value is based on non-missing values and is from the CMH test adjusted for pooled country.

7 Review of Safety

The review of safety will be completed by Dr. Mary Doi. The only safety issue to be addressed in this review will be treatment emergent adverse events (TEAEs) related to seizures and status epilepticus.

Phase 3 Studies

In the phase 3 double-blind pool of patients, the most common event, in all treatment groups, was convulsions. This had a pattern of occurrence similar to

that of all TEAEs related to status epilepticus (preferred term) and convulsions (preferred term). There were no apparent dose-related trends for any of these, while status epilepticus occurred in one subject in the placebo group and two in the total perampanel group. There were no deaths due to status epilepticus.

Convulsion was an SAE in three (0.7%) subjects in the placebo group and six (0.6%) subjects in the total perampanel group (one, three, and two subjects in the 4, 8, and 12 mg/d groups, respectively). This resulted in discontinuation in five (1.1%) placebo treated subjects and 10 (1.0%) perampanel-treated subjects (two, one, four, and three subjects in the 2, 4, 8, and 12 mg/d groups, respectively), and led to dose interruption or reduction in two placebo-treated subjects (0.5%) and two (0.2%) perampanel treated subjects (one each in the 2 and 12 mg/d groups). There were no deaths due to convulsions.

The sponsors table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the phase 3 double blind pool (Safety Analysis set).

Table 37 Convulsions/Status Epilepticus in Phase 3 Studies

MedDRA Preferred Term[b]	Placebo[a] (N=442) n (%)	Perampanel[a] 2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Subjects with any TEAE	25 (5.7)	4 (2.2)	5 (2.9)	22 (5.1)	13 (5.1)	44 (4.2)
Convulsion	16 (3.6)	3 (1.7)	3 (1.7)	15 (3.5)	9 (3.5)	30 (2.9)
Simple Partial Seizures	0	0	1 (0.6)	3 (0.7)	0	4 (0.4)
Grand Mal Convulsion	2 (0.5)	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Status Epilepticus	1 (0.2)	0	0	0	2 (0.8)	2 (0.2)
Postictal Headache	0	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Epilepsy	2 (0.5)	0	1 (0.6)	0	0	1 (0.1)
Aura	0	0	0	1 (0.2)	0	1 (0.1)
Febrile Convulsion	0	1 (0.6)	0	0	0	1 (0.1)
Partial Seizures With Secondary Generalization	0	0	0	1 (0.2)	0	1 (0.1)
Complex Partial Seizures	2 (0.5)	0	0	0	0	0
Postictal Psychosis	1 (0.2)	0	0	0	0	0
Tongue Biting	1 (0.2)	0	0	0	0	0

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.
Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.
MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event
a: Subjects treated during the double-blind study.
b: MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.

Phase 2 Studies

The incidence of the most common event, convulsions, was slightly higher in the placebo group than in the total perampanel group, while status epilepticus occurred in only one (1.5%) subject in the placebo group and one (0.7%) subject in the total perampanel group. There were no deaths and these TEAEs were SAEs in three (4.4%) subjects in the placebo group (one with status epilepticus and two with convulsion) and two (1.3%) subjects in the total perampanel group (one each with status epilepticus and post ictal state). These TEAEs led to discontinuation in two (2.9%) placebo-treated subjects (one each with status epilepticus and convulsion) and one (0.7%) perampanel-treated subject (with status epilepticus). No subject in any treatment group had dose interruption or reduction due to these TEAEs. There were no deaths due to convulsions.

The sponsors table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the phase 2 double blind pool (Safety Analysis set).

Table 38 Convulsions/Status Epilepticus in Phase 2 Studies

MedDRA Preferred Term[b]	Placebo[a] (N=68) n (%)	Perampanel[a] <4 mg/day (N=12) n (%)	4 mg/day (N=101) n (%)	>4-8 mg/day (N=0) n (%)	>8-12 mg/day (N=38) n (%)	Total (N=151) n (%)
Subjects with any TEAE	6 (8.8)	2 (16.7)	5 (5.0)	NA	2 (5.3)	9 (6.0)
Convulsion	3 (4.4)	0	1 (1.0)	NA	2 (5.3)	3 (2.0)
Complex Partial Seizures	0	1 (8.3)	1 (1.0)	NA	0	2 (1.3)
Grand Mal Convulsion	1 (1.5)	1 (8.3)	0	NA	0	1 (0.7)
Partial Seizures	1 (1.5)	1 (8.3)	0	NA	0	1 (0.7)
Status Epilepticus	1 (1.5)	0	1 (1.0)	NA	0	1 (0.7)
Postictal State	0	0	1 (1.0)	NA	0	1 (0.7)
Simple Partial Seizures	0	0	1 (1.0)	NA	0	1 (0.7)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.
Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.
MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, TEAE = treatment-emergent adverse event
a: Subjects treated during the double-blind study.
b: MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.

Convulsions/Status Epilepticus in All Treated Pool

In this group, status epilepticus occurred in 15 (0.9%) subjects in the total perampanel group, compared with two (0.4%) subjects who received placebo in the pooled double-blind studies. The exposure-adjusted rates were 0.0008 and 0.001 subjects per subject-month, respectively. In the analysis by actual dose at onset, this event occurred in three (0.2%) subjects at doses of < 4 mg/d, two (0.1%) subjects at doses of > 4-8 mg/d, and 10 (0.8%) subjects at doses of > 8-12 mg/d. The most common event was convulsion (5.7% of all perampanel-treated subjects), compared with 3.9% in the placebo group from the pooled double-blind studies. The exposure-adjusted rate for this event was 0.01 subjects per subject-month in the placebo group and 0.005 subjects per subject-month in the total perampanel group.

Convulsion was an SAE in five (1.0%) subjects in the placebo group and 31 (1.9%) subjects in the total perampanel group and led to treatment discontinuation in

six (1.2%) and 16 (1.0%) subjects, respectively. There were no deaths due to any TEAEs related to status epilepticus or convulsion.

Although the incidence of status epilepticus in the 12 mg group was higher than that seen in the other dosages, the actual number (2 compared to 0) is too low to draw any meaningful conclusions regarding the possibility of increased seizure activity associated with higher dosages of perampanel. The exposure-adjusted rates suggest that the risk of seizure-related TEAEs, including status epilepticus, was lower with perampanel than with placebo.

The sponsor's table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the all treated pool (safety analysis set).

Table 39 Convulsions/Status Epilepticus in the All Treated Pool

MedDRA Preferred Term[b]	Total Perampanel[a] (N=1639) n (%)
Subjects with any TEAE	147 (9.0)
Convulsion	93 (5.7)
Status Epilepticus	15 (0.9)
Simple Partial Seizures	10 (0.6)
Grand Mal Convulsion	9 (0.5)
Epilepsy	8 (0.5)
Complex Partial Seizures	5 (0.3)
Partial Seizures	4 (0.2)
Postictal Headache	4 (0.2)
Partial Seizures With Secondary Generalization	2 (0.1)
Postictal State	2 (0.1)
Aura	1 (0.1)
Drug Withdrawal Convulsions	1 (0.1)
Epileptic Aura	1 (0.1)
Febrile Convulsion	1 (0.1)
Postictal Psychosis	0
Tongue Biting	0

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.
Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.
MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event
a: Subjects treated with perampanel in any study.
b: MedDRA preferred terms are sorted in descending order of frequency in the total column.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/Reference

None

9.2 Labeling Recommendations

Once daily perampanel doses of 8 mg and 12 mg produced greater reductions in seizure frequency and improved responder rates compared with the once daily dose of 4 mg. However, there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose. The median differences versus placebo in change in seizure frequency during the Maintenance Period for the 8 and 12 mg groups were –16.43% and -15.79%, respectively, while the responder rates were 35.3% and 35.0%, respectively in Study 306. These results were consistent with results for Study 305 and to a lesser extent for Study 304, when analyzed individually.

Additional analyses were performed on the percent change in seizure frequency and responder rate during the Maintenance Period in each randomized dose group using the integrated Full ITT Analysis Set, but excluding subjects from sites in Central and South America (where there was a treatment-by-region interaction of outcome largely due to high placebo response rate). Results of these analyses were consistent in showing better efficacy for the 8 and 12 mg dose groups than for the 4 mg dose group, but no clear separation between these two highest randomized perampanel dose groups.

In contrast to these findings, an analysis of the difference between two doses of perampanel was compared in the same patient who actually received each dose. This approach did show an incremental benefit associated with the 12 mg dose of perampanel over the 8 mg dose. Studies of this design appeared to show benefit from 12 mg over 8 mg. These were derived from examining efficacy responses in subjects who received treatment with both doses, rather than separate groups of subjects.

This reviewer feels that perampanel is safe and effective at doses of 4 mg to 8 mg daily. Some patients might benefit from dosages as high as 12 mg daily, although this could not be clearly demonstrated in the three Phase 3 clinical trials. Additionally, daily dosages of 12 mg are associated with an increased number of adverse side effects, many of which may be unacceptable to patients.

9.3 Advisory Committee Meeting

None

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Medical Review Officer
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/s/

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