# CLINICAL REVIEW

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| Application Type | Supplemental NDA |
| Application Number(s) | 202834/S-005 |
| Priority or Standard | Standard |
| Submit Date(s) | August 19, 2014 |
| Received Date(s) | August 19, 2014 |
| PDUFA Goal Date | June 19, 2015 |
| Division / Office | DNP/ODE-1 |
| Reviewer Name(s) | Philip H. Sheridan, M.D. |
| Review Completion Date | May 15, 2015 |
| Established Name | Perampanel |
| (Proposed) Trade Name | Fycompa |
| Therapeutic Class | Anticonvulsant |
| Applicant | Eisai Inc. |
| Formulation(s) | Oral Tablet 2, 4, 6, 8, 10, 12 mg. |
| Dosing Regimen | 8 mg daily |
| Indication(s) | Adjunctive Treatment of Primary Generalized Tonic Clonic Seizures |
| Intended Population(s) | Patients > 12 years of age with (b) (4) [redacted] |

Template Version:  March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Approval for the adjunctive treatment of primary generalized tonic clonic seizures (PGTC seizures) in patients 12 years of age and above.

## 1.2 Risk Benefit Assessment

Perampanel has been approved since October 22, 2012 for the adjunctive therapy of partial seizures. Its safety profile is known and acceptable for partial seizure patients. Based on the safety results from the pivotal study (E2007-G000-332) for primary generalized tonic clonic seizures, the safety profile is very similar in patients with primary generalized tonic clonic seizures. Perampanel's presumed mechanism of action is unique which would likely make it a valuable addition to the antiepileptic drugs available for treatment of primary generalized tonic clonic seizures. Therefore the risk benefit profile is favorable for approval.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None from clinical review of efficacy

## 1.4 Recommendations for Postmarket Requirements and Commitments

Study of efficacy and safety for primary generalized tonic clonic seizures in children ages 2 years to 12 years (Enrollment of older pediatric patients up to 17 years of age may be needed to ensure adequate patient enrollment)

# 2 Introduction and Regulatory Background

## 2.1 Product Information

The chemical name of perampanel is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile. Perampanel is a noncompetitive, selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. This is presumably the mechanism of action for its antiepileptic effect.

Perampanel has been approved and is currently marketed under the trade name Fycompa® in the United States (October 22, 2012), the European Union (July 23, 2012), and other countries as adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

The purpose of the present submission is to present efficacy and safety data from a single Phase 3 study, Study E2007-G000-332 (hereafter called Study 332), supporting the use of perampanel as adjunctive therapy for the treatment of PGTC seizures in patients with epilepsy aged 12 years and older.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, three antiepileptic drugs (AEDs) (topiramate, levetiracetam, lamotrigine) have demonstrated efficacy in controlled clinical trials and have been approved by the Agency for the adjunctive treatment of PGTC seizures. In addition, valproate is approved for "multiple seizure types which include absence seizures" and is widely used in clinical practice for the treatment of PGTC seizures. Despite the availability of these medications, many patients with PGTC seizures continue to be refractory to treatment. More effective and better tolerated treatment options are needed for this population of medically intractable epileptic patients.

**Table 1 Available Treatments for Primary Generalized Tonic Clonic Seizures**

| Treatment | Approval for PGTC seizures? |
|---|---|
| Topiramate | Yes |
| Levetiracetam | Yes |
| Lamotrigine | Yes |
| Valproate | No |

## 2.3 Availability of Proposed Active Ingredient in the United States

Fycompa tablets are currently approved and marketed in the United States for the adjunctive treatment of partial seizures.

### 2.4 Important Safety Issues With Consideration to Related Drugs

See safety review by Dr. Mary Doi.

Several AMPA antagonists are currently in either preclinical or clinical development in various therapeutic areas. However, no other selective AMPA antagonists are currently approved for any indication.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The epilepsy clinical development program for perampanel for adjunctive treatment of partial seizures included Phase 1 and 2 studies of PK, PD, and tolerability; two Phase 2 studies that provided initial evidence for the anticonvulsant effectiveness of perampanel as adjunctive therapy in a population with POS as well as a potential dose range for this indication; and three Phase 3 double-blind, placebo-controlled studies that provided the primary support for the efficacy of perampanel in POS at the recommended dose range.

The clinical development program for perampanel in PGTC seizures is based on one Phase 3, randomized, double-blind, placebo-controlled study with a long-term OLE (Study 332). The double-blind treatment phase of the study (Core Study) has been completed, and the final efficacy results are presented. The Extension Phase is ongoing;

### 2.6 Other Relevant Background Information

None.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Study E2007-G000-332 has been conducted and reported with adequate quality and integrity.

### 3.2 Compliance with Good Clinical Practices

Study E2007-G000-332 is compliant with Good Clinical Practices.

## 3.3 Financial Disclosures

(b) (6) signed Forms 3454 and 3455.

(b) (6) indicates on Form 3454 that the clinical investigators at the 164 clinical sites (listed as individuals on Attachment 1 of Form 3454) have no disclosable financial arrangements for the E2007-G000-332 study.

(b) (6) indicates on Form 3455 (Disclosure: Financial Interests And Arrangements of Clinical Investigators) that the following listed investigators in study E2007-G000-332 received payments from the sponsor on or after February 2, 1999 such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria:

| Site Number | Investigator | Facility | Number of Subjects | Total Disclosure Amount |
|---|---|---|---|---|
| (b) (6) | | | | $36,432.66 |
| | | | | $47,879.12 |
| | | | | $34,342.03 |
| | | | | $30,914.73 |
| | | | | $35,639.21 |

| | |
|---|---|
| (b) (6) | $26,653.60 |
| | $94,478.11 |
| | $97,465.98 |
| | $36,947.86 |

Attachment 2 to Form 3455 indicates that these listed investigators did not have the potential to influence study results because of the study design (including randomization and blinding) and because of the low number of subjects recruited at their respective sites as shown in the list.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Not applicable.

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

Not applicable.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

Unknown but presumed to be related to [redacted] (b) (4) the AMPA receptor.

#### 4.4.2 Pharmacodynamics

The Sponsor's population PD analysis of the data from Study E2007-G000-332 in patients with primary generalized tonic-clonic seizures suggests that the percent reduction in 28-day average primary generalized tonic-clonic seizure frequency from baseline during maintenance treatment increased as a function of perampanel exposure.

#### 4.4.3 Pharmacokinetics

The Sponsor's population PK analysis based on pooled data from all subjects in Study 332 and the three Phase 3 studies in subjects with refractory partial-onset seizures (Studies 304, 305, 306) in the original application demonstrated that the PK of perampanel was similar in subjects with refractory partial and PGTC seizures and that there was a reduction in perampanel exposure when perampanel was co-administered with the concomitant CYP3A inducers carbamazepine, oxcarbazepine, and phenytoin.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The efficacy and safety of perampanel as adjunctive therapy in PGTC seizures is based on data from a single study, E2007-G000-332 (Study 332).

Study 332 was a double-blind, randomized, placebo-controlled, multicenter, parallel-group study with an open-label extension phase designed to evaluate the efficacy, safety, and PK of perampanel in adolescents (aged ≥12 years) and adults with uncontrolled PGTC seizures despite being maintained on a stable dose of 1 to a maximum of 3 AEDs.

### 5.2 Review Strategy

I have reviewed the clinical study report (CSR) for Study E2007-G000-332, the clinical overview, and the summary of clinical efficacy provided by the Sponsor. The primary analysis of efficacy was independently verified in the Statistical Review by Dr. Xiang

Ling who also provided a sensitivity analysis and analyses of efficacy by patient subgroups. The safety data have been reviewed in a separate review by Dr. Mary Doi.

### 5.3 Discussion of Individual Studies/Clinical Trials

There is only one efficacy study (E2007-G000-332) which is discussed in Section 6 of this review.

# 6 Review of Efficacy

***Efficacy Summary***

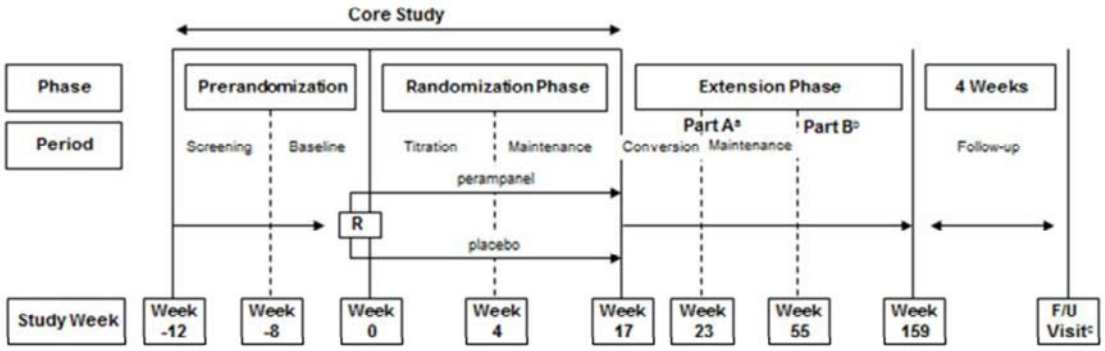
### 6.1 Indication

Adjunctive treatment of primary generalized tonic clonic seizures (PGTC seizures) in patients 12 years of age and above.

#### 6.1.1 Methods

Study E2007-G000-332 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, adjunctive therapy study in subjects 12 years of age and older with PGTC seizures. The study consisted of 3 phases: Prerandomization, Randomization, and Extension (Figure 1).

**Figure 1 Study Design of Study 332**




R = Randomization.
F/U = Follow-up.
a = All subjects should be retained in the study through the last visit of Extension Part A.
b = Subjects only need to complete Part B if perampanel is not made available free of charge according to the appropriate local country-specific mechanism (revised per Amendment 03)
c = The Follow-up visit should be conducted for all subjects 4 weeks after their last on-treatment visit.

The Prerandomization Phase consisted of 2 periods: Screening and Baseline, during which subjects were assessed for their eligibility to participate in the study.

The Randomization Phase consisted of 3 periods: Titration, Maintenance, and Follow-up (only for those subjects not entering the Extension Phase).

At the start of the Randomization Phase, eligible subjects were randomized to the perampanel (2 to 8 mg/d) or placebo treatment groups in a 1:1 ratio.

The Extension Phase consisted of 2 parts: Part A (blinded Conversion Period and Maintenance) and Part B (optional; Maintenance).

**Core Study: Prerandomization Phase**

The Prerandomization Phase was up to 12 weeks in duration, during which subjects were assessed for overall eligibility to participate in the study, including seizure activity.

The Prerandomization Phase consisted of 2 periods: Screening Period (up to 4 weeks, depending on how soon the required documentation was obtained) and Baseline Period (4 or 8 weeks, depending on the accuracy of diary-documented seizure frequency during the Screening Period).

The Screening Period commenced with Visit 1, at which time subject consent/assent was obtained and assessments were performed to determine subject eligibility. Eligible subjects had a clinical diagnosis of PGTC seizures (with or without other subtypes of

primary generalized seizures), confirmed by electroencephalogram (EEG). Subjects who met all of the inclusion and none of the exclusion criteria at Visit 1 were given a subject seizure diary to be used for recording seizure count and type on a daily basis. The diary was to be completed daily, by either the subject or designated caregiver, and all seizures were to be recorded. Subjects must have had at least 8 weeks of consecutive seizure diary data before randomization (up to 4 weeks could have been obtained from the subject's personal retrospective seizure diary if collected immediately before study entry). To qualify for randomization, subjects must have experienced at least 3 PGTC seizures during the Baseline Period, as recorded in the seizure diary.

Eligible subjects were receiving stable, fixed doses of 1 to a maximum of 3 approved AEDs for a minimum of 30 days before Baseline. Only 1 AED could have been an inducer AED (defined in the protocol as carbamazepine, oxcarbazepine, or phenytoin). Eslicarbazepine was recently approved in Europe (in 2009) and the US (in 2013) as an adjunctive therapy for POS. Eslicarbazepine was to be coded as an inducer AED in Study 332, but this was not necessary because none of the subjects were prescribed this drug as a concomitant AED.

***Reviewer Note:***

***Because those antiepileptic drugs which act as sodium channel blockers have been reported to exacerbate other seizure types associated with PGTC seizures (myoclonic and absence seizures), these antiepileptic drugs (which also are the antiepileptic drugs acting most significantly as inducers) are not usually used in the PGTC seizure population. For this reason, there is little experience from Study 332 on which to base labeling language regarding concomitant use of inducer antiepileptic drugs.***

A review was conducted by an independent epilepsy expert group (Epilepsy Study Consortium) of information provided by the investigator regarding the diagnosis and seizure type for each subject who provided informed consent. Only when the accuracy of the diagnosis was approved by the Epilepsy Study Consortium was a subject eligible for participation in the study.

**Core Study: Randomization Phase**

The Randomization Phase was up to 21 weeks in duration, and consisted of 3 periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up (4 weeks, only for those subjects not entering the Extension Phase). Subjects whose screening assessments and evaluations were completed and reviewed by the investigator, and who continued to meet all of the inclusion and none of the exclusion criteria, entered the Randomization Phase.

Eligible subjects were randomized in 1:1 ratio to receive perampanel or perampanel-matched placebo.

Subjects continued to take their baseline AED medication regimen throughout the Randomization Phase, and subjects or their designated caregivers continued to complete the subject diary each day.

Titration Period

The Titration Period was 4 weeks in duration (Weeks 1-4). During the Titration Period, all subjects took 6 tablets (initially 1 tablet of 2-mg perampanel + 5 tablets of perampanel-matched placebo [perampanel group] or 6 tablets of perampanel-matched placebo [placebo group]). For the perampanel group, the dose was increased (by replacing perampanel-matched placebo tablets with perampanel tablets) at weekly intervals in increments of 2 mg to the target dose of 8 mg/day or highest tolerated dose. Upon completion of the Titration Period, subjects began the Maintenance Period.

**Maintenance Period**

The Maintenance Period was 13 weeks in duration (Weeks 5-17). During the Maintenance Period, subjects continued treatment with the study drug dose achieved during the Titration Period, taking the study drug once daily in a blinded fashion.

Dose adjustment during the Maintenance Period was not recommended. According to the investigators' clinical judgment, however, subjects with inadequate seizure control were allowed to have their dose increased by one 2 mg increment, and subjects experiencing intolerable AEs were allowed to have their dose down-titrated by only 2 mg during the Maintenance Period. More than 1 up-titration or down-titration was not allowed during the Maintenance Period unless there was a significant medical reason and the change was approved by the Medical Monitor.

The maximum dose of the study drug during the Randomization Phase was 8 mg/day.

Subjects who completed the Randomization Phase could enter the Extension Phase and receive open-label perampanel. Subjects who did not continue into the Extension Phase proceeded to the Follow-up Period.

**Follow-Up Period**

At the end of the 4-week Follow-up Period, subjects returned to the clinical site and underwent all End-of-Study (EOS) procedures. Subjects who discontinued from the study prematurely underwent the EOS procedures at the time of discontinuation as well as at the end of the Follow-up Period.

The Extension Phase is ongoing (b) (4)

**Study Treatments (Dose selection)**

The efficacy and safety of perampanel doses up to 12 mg/day were demonstrated in randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies (Studies E2007-G000-304, E2007-G000-305, and E2007-G000-306) in subjects with partial seizures. These studies established a positive benefit to risk profile for the use of perampanel at doses up to 12 mg/day as adjunctive therapy for POS.

Dose selection for the PGTC Core Study 332 was principally driven by the anticipated efficacy and tolerability of 8-mg/day of perampanel in subjects with PGTC seizures based on effects previously observed on secondary generalized seizures in the POS Phase 3 studies.

Subjects requiring additional seizure control were given the option to increase their dose to 12 mg/day in the Extension Phase only.

***Reviewer Note:***

***There was only one treatment arm which had a targeted dose of 8 mg/day. Because, in general, patients with PGTC seizures respond to a lower dose of an antiepileptic drug compared to patients with partial seizures and because PGTC seizure patients rarely use inducers as concomitant antiepileptic drugs, the Sponsor did not include a 12 mg/day treatment arm.***

***Dr. Mary Doi, the safety reviewer, verified that the majority of patients in the treatment arm received the full 8 mg dose, concluding:***

> ***While the maximum daily dose received was 8 mg for most perampanel subjects (95.1%, n=77), the last dose received was 8 mg for 84.0% of the perampanel subjects (CSR 332 Core, Table 14.3.1.1.9). Of the 77 subjects who received the maximum dose of 8 mg, down-titrating or discontinuations occurred in 24.7% (n=19) (CSR 332 Core, Table 14.3.1.1.16). For most of these subjects, the dose reduction or discontinuation was due to a TEAE (73.7%, n=14) or subject choice (15.8%, n=3).***

**Study Population: Inclusion/Exclusion Criteria**

**Key inclusion criteria for the Core Study were:**

• Age 12 years and older.

• Clinical diagnosis of PGTC seizures in the setting of idiopathic generalized epilepsy (with or without other subtypes of primary generalized seizures) and experiencing greater than or equal to 3 PGTC seizures during the 8-week period before randomization.

• Routine EEG up to 5 years before or during the Baseline Period with electroencephalographic features consistent with primary generalized epilepsy.

• A fixed dose of 1 to a maximum of 3 concomitant AEDs for a minimum of 30 days before Baseline Period; only 1 inducer AED (ie, carbamazepine, oxcarbazepine, or phenytoin) out of the maximum of 3 AEDs was allowed.

**Key exclusion criteria were:**

• Participation in previous perampanel study(ies).

• History of status epilepticus that required hospitalization within 12 months before baseline.

• Concomitant diagnosis of POS.

• Clinical diagnosis of Lennox-Gastaut syndrome.

• History of seizure clusters where individual seizures could not be counted.

• Concomitant use of medications known to be inducers of the isoform of cytochrome P450 [subfamily 3A] (CYP3A), with the exception of carbamazepine, oxcarbazepine, and phenytoin) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin, within 30 days before Baseline or were receiving concomitant barbiturates (except for seizure control indication) within 30 days before baseline.

• Use of rescue benzodiazepines intermittently (ie, 1 to 2 doses over a 24-h period was considered 1-time rescue) more than 2 times within the 30 days before baseline.

Key Extension Phase inclusion criteria were patients who:

• Completed Visit 8 of the Core Study and showed compliance with the inclusion and

exclusion criteria for that study (excluding criteria that were related to seizure occurrences).

• Continued to be treated with a stable dose of 1 to a maximum of 3 approved AEDs.
Subjects were not eligible to participate in the Extension Phase if they had discontinued early from the Core Study for any reason.

### 6.1.2 Demographics

Demographic characteristics for the Full Analysis Set (modified intent to treat population) are summarized in Table 2. The mean age of the population was 28.4 years (range, 12 to 70 years); 11.1% of the subjects were ≥12 to <17 years old, 13.6% of the subjects were ≥12 to <18 years old, and 1 subject (0.6%) was 65 years or older. Approximately half of the subjects were white. There were slightly more females (56.2%) than males (43.8%). The mean weight was 70.66 kg, and the mean body mass index (BMI) was 24.982 kg/m2. Baseline demographic characteristics were balanced between the placebo and perampanel treatment groups.

**Table 2 Demography and Baseline Characteristics of Full Analysis Set**

| Category | Placebo (N=81) | Perampanel (N=81) | Combined Total (N=162) |
|---|---|---|---|
| Age (year)a | | | |
| n | 81 | 81 | 162 |
| Mean (SD) | 29.5 (12.19) | 27.3 (10.54) | 28.4 (11.42) |
| Median | 26.0 | 26.0 | 26.0 |
| Min, Max | 14, 70 | 12, 58 | 12, 70 |
| Age group (1), n (%) | | | |
| <17 years | 7 (8.6) | 11 (13.6) | 18 (11.1) |
| ≥17 to <65 years | 73 (90.1) | 70 (86.4) | 143 (88.3) |
| ≥65 years | 1 (1.2) | 0 | 1 (0.6) |
| Age group (2), n (%) | | | |
| <18 years | 9 (11.1) | 13 (16.0) | 22 (13.6) |
| ≥18 to <65 years | 71 (87.7) | 68 (84.0) | 139 (85.8) |
| ≥65 years | 1 (1.2) | 0 | 1 (0.6) |
| Sex, n (%) | | | |
| Male | 36 (44.4) | 35 (43.2) | 71 (43.8) |
| Female | 45 (55.6) | 46 (56.8) | 91 (56.2) |

| | | | |
|---|---|---|---|
| Race, n (%) | | | |
| White | 43 (53.1) | 44 (54.3) | 87 (53.7) |
| Black or African American | 3 (3.7) | 1 (1.2) | 4 (2.5) |
| Japanese | 6 (7.4) | 5 (6.2) | 11 (6.8) |
| Chinese | 18 (22.2) | 18 (22.2) | 36 (22.2) |
| Other Asian | 10 (12.3) | 11 (13.6) | 21 (13.0) |
| Other | 1 (1.2) | 2 (2.5) | 3 (1.9) |

Percentages are based on the total number of subjects with non-missing values in relevant treatment group. Max = maximum; Min = minimum; SD = standard deviation.
Group (1) = Age distributions of ≥12 y to <17 y, ≥17 y to <65 y, and ≥65 y.
Group (2) = Age distributions of ≥12 y to <18 y, ≥18 y to <65 y, and ≥65 y. a: Age is calculated at date of Informed Consent.
Source: Core Study 332 CSR, Table 14.1.4.1.1.

***Reviewer Note:***

***Only 11.1% of the full analysis set were in the pediatric age group (less than 17 years of age), and only 11 pediatric patients received perampanel in this study. Thirteen patients less than 18 years of age received perampanel. As discussed in section 6.1.7 of my review, the statistical reviewer (Dr. Xiang Ling) performed an efficacy analysis of the pediatric subgroup which indicates efficacy in this pediatric subpopulation.***

### 6.1.3 Subject Disposition

A total of 164 subjects were randomized. One perampanel subject did not receive any study drug and one placebo subject did not have post-baseline seizure data and was thus excluded from the full analysis set (FAS) population which is the modified intent to treat (mITT) population (162 subjects) consisting of all randomized subjects who received at least one dose of study medication and had any post-baseline seizure frequency data.

The Core Study completion rate was 87.8% and 84.0% for the placebo and perampanel groups, respectively. The most common reason for discontinuation was adverse events (AEs): 9 (11.1%) subjects in the perampanel group were discontinued due to an AE compared with 5 (6.1%) subjects in the placebo group.

**Core Study**

Disposition information for all randomized subjects is summarized in Table 3. For the treated subjects, the completion rates were comparable in the placebo group (87.8%) and the perampanel group (84.0%). The most common primary reason for discontinuation in both treatment groups was AEs, which was the primary reason for

discontinuation of a higher percentage of subjects in the perampanel group (11.1%) than the placebo group (6.1%).

**Table 3 Subject Disposition and Primary Reason for Discontinuation**

| | Placebo | Perampanel |
|---|---|---|
| **Randomized, n** | 82 | 82 |
| Not treated, n | 0 | 1 |
| **Treated, n (%)** | 82 (100.0) | 81 (100.0) |
| Completed Core Study, n (%) | 72 (87.8) | 68 (84.0) |
| Discontinued from Core Study, n (%) | 10 (12.2) | 13 (16.0) |
| | | |
| Primary reason for discontinuation[a], n (%) | | |
| Adverse event | 5 (6.1) | 9 (11.1) |
| Lost to follow up | 1 (1.2) | 1 (1.2) |
| Subject choice | 2 (2.4) | 3 (3.7) |
| Inadequate therapeutic effect | 2 (2.4) | 0 |
| Pregnancy | 0 | 0 |
| Other | 0 | 0 |

Percentages are based on the number of subjects randomized and treated in the relevant treatment group. a: As reported on the Subject Disposition Core Case Report Form.
Source: Core Study CSR, Table 14.1.1.3.

***Reviewer Note:***

***Dropouts and discontinuations are discussed in detail in the Safety review by Dr. Mary Doi.***

## 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the percent change from baseline in PGTC seizure frequency per 28 days during treatment (Titration + Maintenance), except for the purpose of European Union (EU) registration where this endpoint was the key secondary efficacy endpoint. Seizure frequency per 28 days was derived from the information recorded in the subject diaries. The percent change from baseline was analyzed over the Titration and Maintenance Periods combined, while baseline was defined as seizure frequency per 28 days based on all valid diary data during the Prerandomization Phase.

## Results

## Total Efficacy Population

The median percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Pre-randomization was greater with perampanel (-76.47%) than with placebo (-38.38%). The estimated median treatment difference to placebo of -30.81% was statistically significant (P<0.0001), indicating a significant improvement in the reduction of PGTC seizure frequency for the perampanel group compared to placebo.

**Table 4 PGTC Sz Frequency per 28 Days and Percent Change During Treatment**

| | Placebo (N=81) | | Perampanel (N=81) | |
|---|---|---|---|---|
| **Statistic** | **Actual** | **Percent Change** | **Actual** | **Percent Change** |
| n | 81 | 81 | 81 | 81 |
| Mean (SD) | 2.87 (4.74) | -5.85 (184.56) | 1.90 (3.30) | -56.88 (50.76) |
| Median | 1.57 | -38.38 | 0.71 | -76.47 |
| Min, Max | 0.0, 39.1 | -100.0, 1546.3 | 0.0, 22.8 | -100.0, 184.5 |
| Median Difference to Placebo | | | | -30.81 |
| (95% Confidence Interval) | | | | (-45.49, -15.24) |
| *P* value compared to Placebo | | | | <.0001 |

***Source: Statistical review by Dr. Xiang Ling***

## Sensitivity Analyses for the Primary Endpoint by the Agency's Statistical Reviewer

The findings of the primary analysis were supported by sensitivity analyses (performed by the Agency's statistical reviewer, Dr. Xiang Ling) using different analysis populations (Per Protocol Analysis Set and completer set) and a different study period (Maintenance Period alone rather than the combined Titration and Maintenance periods used in the Sponsor's protocol).

Dr. Ling conducted an additional sensitivity analysis on the ITT population using nonparametric ANCOVA. The result was consistent with the primary analysis performed by the Sponsor.

In the Sponsor's primary analysis, only seizure data up to the date of the last dose were used to calculate seizure frequency for subjects who dropped out early. Since some patients still reported seizure status even though they stopped taking the study drug, Dr. Ling conducted an analysis in which all available seizure data were used. The result was almost identical with that of the primary analysis by the Sponsor. The estimated median treatment difference from placebo was -29.01% (P<0.0001).

For a worst-case type of analysis, Dr. Ling imputed the seizure frequency for dropouts in the perampanel group using baseline seizure frequency. The result still favored the perampanel group (P=0.0008).

***Reviewer Comment:***

***Dr. Ling concluded that the findings of the primary efficacy analysis were supported by sensitivity analyses including worst-case type of analyses. Thus, the efficacy findings are robust enough to justify granting the indication for adjunctive therapy of PGTC seizures based on a single study (Study 332).***

### 6.1.5 Analysis of Secondary Endpoints(s)

The primary efficacy endpoint for EU registration was the 50% responder rate in the Maintenance Period relative to baseline. For all other purposes, this was the key secondary endpoint. Responders were defined as subjects who experienced a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance Period relative to baseline (Prerandomization Phase).

The PGTC seizure frequency per 28 days (as determined from subject diaries) was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28.

Table 5 summarizes the PGTC responder rates during the Maintenance Period for the Full Analysis Set. The percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was 39.5% in the placebo group and 64.2% in the perampanel group (P=0.0019).

**Table 5 PGTC Seizure 50% Responder Rate During Maintenance**

| | Placebo (N=81) | Perampanel (N=81) |
|---|---|---|
| **Responder** | | |
| Yes, n (%) | 32 (39.5) | 52 (64.2) |
| No, n (%)[- | 49 (60.5) | 29 (35.8) |
| Total | 81 (100.0) | 81 (100.0) |
| *P* value compared to Placebo | | 0.0019 |

***Source: Statistical review by Dr. Xiang Ling***

Another secondary endpoint examined the effect of perampanel on other seizure subtypes (absence and myoclonic seizures) associated with PGTC seizures. This endpoint is discussed in section 6.1.10 of this review.

### 6.1.6 Other Endpoints

None

### 6.1.7 Subpopulations

Percent changes in Seizure Frequency by Age Group, Gender, Race, and Geographic Region

The analysis for the primary endpoint by demographic subgroups (with at least one subject in each treatment group) was performed by the Agency's statistical reviewer (Dr. Xiang Ling). The analysis results are presented in Table 6. Dr Ling concluded that the treatment effect was generally consistent across the subgroups.

**Table 6 Percent Change in Sz Frequency by Age, Sex, Race, Geographic Region**

| | Placebo | Perampanel |
|---|---|---|
| Age Group: <18 Years | | |
| n | 9 | 13 |
| Median (%) | -29.84 | -88.03 |
| Min, Max (%) | -100.0, 153.6 | -100.0, 184.5 |
| Age Group: >=18 to <65 Years | | |
| n | 71 | 68 |
| Median (%) | -38.38 | -74.37 |
| Min, Max (%) | -100.0, 1546.3 | -100.0, 108.8 |

| | | |
|---|---|---|
| Sex: Male | | |
| n | 36 | 35 |
| Median (%) | -24.93 | -53.33 |
| Min, Max (%) | -100.0, 1546.3 | -100.0, 184.5 |
| Sex: Female | | |
| n | 45 | 46 |
| Median (%) | -41.67 | -83.00 |
| Min, Max (%) | -100.0, 153.6 | -100.0, 108.8 |
| Race: White | | |
| n | 43 | 44 |
| Median (%) | -43.53 | -65.48 |
| Min, Max (%) | -100.0, 1546.3 | -100.0, 108.8 |
| Race: Black/African American | | |
| n | 3 | 1 |
| Median (%) | 1.85 | -100.00 |
| Min, Max (%) | -3.4, 8.5 | 100.0, -100.0 |
| Race: Asian/Pacific | | |
| n | 34 | 34 |
| Median (%) | -27.94 | -79.05 |
| Min, Max (%) | -100.0, 125.7 | -100.0, 184.5 |
| Race: Other | | |
| n | 1 | 2 |
| Median (%) | -54.80 | -62.12 |
| Min, Max (%) | -54.8, -54.8 | -100.0, -24.2 |
| Region: North America | | |
| n | 19 | 19 |
| Median (%) | -38.79 | -76.67 |
| Min, Max (%) | -88.8, 1546.3 | -100.0, 108.8 |
| Region: Europe | | |
| n | 20 | 20 |
| Median (%) | -31.85 | -80.60 |
| Min, Max (%) | -100.0, 141.5 | -100.0, 22.4 |
| Region: Asia-Pacific | | |
| n | 42 | 42 |
| Median (%) | -38.38 | -66.77 |
| Min, Max (%) | -100.0, 125.7 | -100.0, 184.5 |

**Source: Statistical review by Dr. Xiang Ling**

***Reviewer Comment:***

***In the pediatric subpopulation, only 11 patients under the age of 17 years received perampanel and only 13 patients under the age of 18 years received perampanel. Although it appears that there is similar evidence of efficacy in the pediatric subpopulation as in the mITT population as a whole, additional pediatric study of perampanel would be desirable.***

***The initial pediatric study plan for FYCOMPA requires a study of efficacy and safety for younger children ages 2 years to 12 years. It is likely that this study will also include older children up to the age of 17 years and will thus provide additional evidence of efficacy in the pediatric population.***

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 4.4 of this review.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Sponsor did not look for evidence of tolerance during the double blind, placebo-controlled maintenance phase. To examine the maintenance phase for evidence of tolerance, I asked the Agency's statistical reviewer Dr. Ling to prepare a table of descriptive statistics which looked at the last 12 weeks of the 13 week maintenance period by dividing it into three 4-week epochs and comparing the efficacy response at for each epoch (Table 7). The total 13 week maintenance period was from week 5 to week 17 (post randomization); therefore the three epochs were weeks 6-9, weeks 10-13, and weeks 14-17.

**Table 7 Comparison of Efficacy in the Early, Mid, and Late Epochs of the Study 332 Maintenance Period to Examine for Tolerance to Efficacious Effect**

| | Placebo (N = 81) | | Perampanel (N = 81) | |
|---|---|---|---|---|
| **Analysis Window, Statistic** | **Actual** | **Percent Change** | **Actual** | **Percent Change** |
| **Weeks 6 - 9** | | | | |
| n | 78 | 78 | 77 | 77 |
| Mean (SD) | 2.61 (3.825) | -20.71 (79.900) | 1.54 (2.280) | -60.74 (49.485) |
| Median | 2.00 | -33.93 | 0.90 | -78.52 |
| Min, Max | 0.0, 29.2 | -100.0, 337.0 | 0.0, 12.0 | -100.0, 72.6 |
| | | | | |
| **Weeks 10 - 13** | | | | |
| n | 75 | 75 | 70 | 70 |
| Mean (SD) | 2.73 (8.932) | 1.96 (373.206) | 1.67 (3.575) | -64.16 (51.178) |
| Median | 1.00 | -47.62 | 0.00 | -100.00 |
| Min, Max | 0.0, 77.0 | -100.0, 3145.0 | 0.0, 24.0 | -100.0, 72.4 |
| | | | | |
| **Weeks 14 - 17** | | | | |
| n | 73 | 73 | 68 | 68 |
| Mean (SD) | 2.95 (8.253) | 4.09 (341.445) | 1.22 (2.458) | -71.10 (42.940) |
| Median | 1.04 | -37.78 | 0.00 | -100.00 |
| Min, Max | 0.0, 69.6 | -100.0, 2832.1 | 0.0, 15.0 | -100.0, 108.3 |

The difference between the placebo arm and the perampanel arm in the percent change in PGTC seizure frequency per 28 days persisted unchanged from the early epoch to the late epoch of the maintenance phase. There is no evidence for the development of tolerance to the efficacious effect of perampanel.

The Sponsor did look for evidence of tolerance during the Open Label Extension Phase. Because this phase is still ongoing, the Sponsor reported interim findings on persistence of efficacy during the Open Label Extension Phase as shown in Table 8.

**Table 8 Percent Change from Core Study Prerandomization Phase in PGTC Seizure Frequency per 28 Days and Responder Rate in Ongoing Extension Phase**

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

Week 1 began on the date of first dose of perampanel treatment duration. The perampanel treatment duration started from the first perampanel dose in the Core Study or Extension Phase and continued to and included the date of the last dose of perampanel in the Extension Phase. In Part B of the Extension Phase (after Visit 15), the seizure diary was only completed for days on which a seizure occurred. For purposes of the analysis, zero was imputed for non-seizure days. For any given analysis window and seizure type(s), a 50% responder from pre-perampanel was a subject whose seizure frequency per 28 days for that seizure type(s) during that analysis window was 50% to 100% lower than the pre-perampanel baseline seizure frequency per 28 days for that same seizure type(s).
n = number of subjects with event; PGTC = primary generalized tonic-clonic.

Table 8 (from the Sponsor's Summary of Clinical Efficacy) summarizes, by previous double-blind treatment group (placebo or perampanel), the median percent change in PGTC seizure frequency per 28 days and the percentage of PGTC 50% responders for the Core Study Maintenance Period (when dose was stable), the blinded Conversion Period of the Extension Phase, and by 13-week intervals through Weeks 79 to 91 for the Maintenance Period of the Extension Phase. Among subjects who received prior double-blind treatment with placebo, both the median percent reduction in PGTC seizure frequency and the PGTC 50% responder rate increased to a level similar to that

for subjects receiving previous double-blind treatment with perampanel by the end of the blinded Conversion Period of the Extension Phase. Among subjects who received prior double-blind treatment with perampanel, reduction in PGTC seizure frequency and PGTC 50% responder rate was similar or greater in the Extension Phase. The median percent change in seizure frequency indicates efficacy established in the Core Study was maintained during the Extension Phase.

***Reviewer Note:***

***Both the double-blind placebo-controlled data from the maintenance phase and the open label interim data to date from the Open Label Extension Phase suggest that the efficacious effect of perampanel is persistent and that tolerance is not a problem. Tolerance to perampanel has not been reported in the treatment of partial seizures, so it was not expected in the treatment of PGTC seizures. More complete information will be available when the Open Label Extension Phase is concluded.***

### 6.1.10 Additional Efficacy Issues/Analyses: Effect of Perampanel on Other Seizure Subtypes (Absence and Myoclonic Seizures)

Although the other antiepileptic drugs that have been approved for PGTC seizures have not caused an exacerbation of the other seizure subtypes associated with PGTC seizures, there is a concern that a new antiepileptic drug with a presumably new mechanism of action such as perampanel might have this adverse effect in the PGTC seizure patient population. Such an exacerbation has been reported from antiepileptic drugs which act as sodium channel blockers.

Therefore, another secondary efficacy endpoint was the percent change in other subtypes of primary generalized seizure frequency (i.e., absence or myoclonic) per 28 days in the Titration and Maintenance Periods combined relative to baseline.

The sponsor reports that only a minority of subjects in the Titration and Maintenance Periods combined experienced absence (60/162, 37.0%) or myoclonic (47/162, 29.0%) seizures during the Prerandomization Phase and were included in the analyses of these secondary endpoints. The estimated median percent decrease in absence seizures was greater for the perampanel group than the placebo group (-41.2% vs -7.6%; P=0.3478). For myoclonic seizures, the baseline rate in the placebo group was markedly lower than in the perampanel group (3.5 vs. 13.8) and the estimated median percent change was greater in the placebo group (-52.5% vs -24.5%; P=0.6100). The numerically larger median percent reduction in myoclonic seizures for the placebo group is likely related to the nearly 4-fold lower median frequency of these seizures during the Prerandomization Phase in the placebo group compared with the perampanel group (3.5 vs 13.8). Given

the substantially lower myoclonic seizure frequency in the placebo group at baseline, any change in the occurrence of this seizure type postbaseline would result in a large percentage change value.

***Reviewer Comment:***

***The key observation is that, in those patients who also had either absence or myoclonic seizures in addition to PGTC seizures in the baseline period, the rate of both of these seizure subtypes was lower in the treatment period than in the baseline period. This indicates that perampanel did not exacerbate either absence or myoclonic seizures. The observation that the median percent reduction from baseline for myoclonic seizures was greater for placebo patients than for perampanel patients is probably due to the low median frequency of myoclonic seizures for placebo patients during baseline and the relatively small population size of total patients who had myoclonic seizures during the baseline period.***

***Since only the subsets of patients who had absence seizures or myoclonic seizures were included in the Sponsor's analysis for exacerbation of these seizure subtypes, I asked the Agency's safety reviewer Dr. Mary Doi to ascertain if any patients that did not have these two seizure subtypes during baseline had these seizures during the treatment period. Six such patients had absence seizures in the treatment period: 3 on placebo and 3 on perampanel. Four such patients had myoclonic seizures in the treatment period: 2 on placebo and 2 on perampanel. Only one patient in the study is coded as having had "exacerbation of seizures" as a severe adverse effect requiring hospitalization; this brief hospitalization (of a patient on 8 mg of perampanel) occurred due to a single moderate to severe PGTC seizure attributed to a subtherapeutic level of his concomitant drug (valproate).***

# 7 Review of Safety

See Safety Review by Dr. Mary Doi.

# 8 Postmarket Experience

The recent post-marketing experience for the adjunctive therapy of partial onset (focal) seizures (including the 120 day safety update report submitted in December 2014) is addressed in detail in the Safety Review of this submission by Dr. Mary Doi.

# 9 Appendices

## 9.1 Literature Review/References

None.

## 9.2 Labeling Recommendations

Draft labeling is being negotiated with the Sponsor.

## 9.3 Advisory Committee Meeting

Not applicable.

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PHILIP H SHERIDAN
06/09/2015

NORMAN HERSHKOWITZ
06/09/2015