U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	202834/S-005
Drug Name:	FYCOMPA® (perampanel)
Indication(s):	primary generalized tonic-clonic (PGTC) seizures
Applicant:	Eisai
Date(s):	Submission date: 08/19/14
	PDUFA Date: 06/19/2015
Review Priority:	Standard Review
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1 EXECUTIVE SUMMARY

The data overall provided evidence to support for the efficacy of perampanel as adjunctive treatment in adult and adolescent subjects with previously inadequately controlled PGTC seizures. Study results indicate that patients in perampanel group were statistically significantly better than patients in placebo, with respect to the primary efficacy endpoint (percent change in PGTC seizure frequency) and the key secondary endpoint (50% PGTC responder rate). The findings of the primary efficacy analyses were supported by sensitivity analyses including worst-case type of analyses. The effect of perampanel was generally consistent across demographic subgroups.

2 INTRODUCTION

2.1 Overview

The sNDA included a single Phase 3 study, Study E2007-G000-332 (Study 332) to support a new indication for FYCOMPA® (perampanel) tablets as adjunctive therapy for the treatment of primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\NDA202834\0089 and \\CDSESUB1\evsprod\NDA202834\0096.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Key efficacy endpoints were reproduced by this reviewer from raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant’s key efficacy results.

3.2 Evaluation of Efficacy

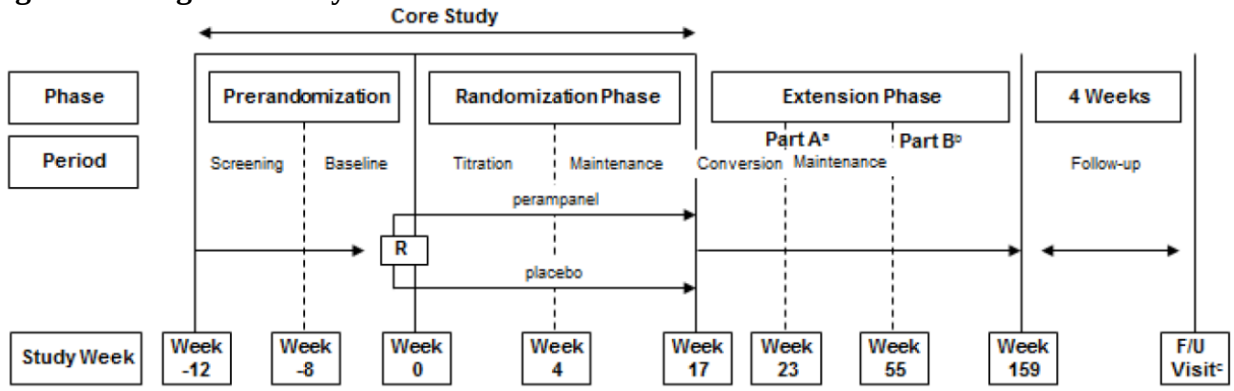
3.2.1 Study Design and Endpoints

The first subject was enrolled in Study 332 on July13, 2011 and the last subject visit in the Core Study was May 27, 2014. The protocol was amended 3 times and the last version was dated November 15, 2013. The statistical analysis plan (SAP) was finalized on May 21, 2014, and the database for the Core Study was locked on June 04, 2014.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, adjunctive-therapy study with an open-label Extension Phase. The Core Study consisted of 2 phases: Pre-randomization and Randomization. The Pre-randomization Phase consisted of 2 periods: Screening (up to 4 weeks) and Baseline (4 or 8 weeks), during which subjects were assessed for their eligibility to participate in the study. Eligible subjects were randomized to the perampanel (2 to 8 mg per day) or placebo treatment groups in a 1:1 ratio. The Randomization Phase consisted of 3 periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up for subjects not entering into the Extension Phase (4 weeks). Approximately 164 subjects with PGTC seizures were planned for enrollment at approximately 95 sites in the US, Europe, and Asia. Males and females 12 years and older who had a diagnosis of PGTC seizures, receiving one to a maximum of three anti-epileptic drugs (AEDs), and experiencing >=3 PGTC seizures during the Baseline Period were included in this trial.

Figure 1. Design for Study E2007-G000-332



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.

Source: CSR Figure 1.

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Efficacy Endpoints
The primary endpoint was the percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods combined relative to baseline.

The key secondary endpoint was the 50% responder rate in the Maintenance Period (that is, ≥50% reduction in PGTC seizure frequency during the Maintenance Period relative to baseline)

3.2.2 Statistical Methodologies

Efficacy Analysis Population
The efficacy analysis set was Full Analysis Set (FAS), consisting of all randomized subjects who received at least one dose of study medication and had any post-baseline seizure frequency data.

Analysis of the Primary Endpoint
For the analysis of percent change in PGTC seizure frequency, the baseline seizure frequencies per 28 days and the percent change per 28 days across the Titration and Maintenance Periods combined were rank transformed separately. An analysis of covariance (ANCOVA) was conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline PGTC seizure frequency per 28 days as a covariate. The treatment difference was estimated using the Hodges-Lehmann estimator and associated 95% confidence interval (CI).

Only "valid days" and "valid seizure counts" were used in the calculations of seizures frequency per 28 days. A "valid day" was defined as the day where seizure counts information is present, that is, either a record with an answer of 'No' to the question 'Did the subject experience'.

Countries in each geographic region (US, Europe, and Asia) were pooled per SAP so that each of these countries have at least 6 subjects (the pooled countries are: Austria/Greece/Serbia/Israel; Lithuania/France; Czech Republic/Poland; all other countries were not pooled).

Sensitivity Analyses for the primary endpoint
The percent change in PGTC seizure frequency during the Maintenance Periods was assessed. For patients who dropped out early, if the overall duration of the Maintenance Period was less than 8 weeks, the diary data from the last 8 weeks (or all available diary data if less than 8 weeks) of the treatment duration (Titration Period + Maintenance Period) was used to calculate the seizure frequency.

The primary analysis was also repeated on the Per Protocol Analysis Set and the Completer set.

Analyses of the Key Secondary Endpoints
Responder rates were analyzed using the Cochran−Mantel−Haenszel test stratified by pooled country. The Maintenance period (using data from last 8 weeks of treatment duration for subjects dropped out early) was used for this analysis.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 164 subjects were randomized. One subject did not receive any study drug and one subject did not have post-baseline seizure data and was thus excluded from the FAS population. 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 (Table 1).

Table 1. Subject Disposition

	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, 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

Source: Table 4 of the CSR.

The perampanel and placebo groups were comparable with respect to demographic and baseline disease characteristics. The majority of subjects were White (53.7%), female (56.2%), and between the ages of 18 and 64 years (85.8%). The treatment groups were comparable with respect to seizure frequency during the Pre-randomization phase (Table 2).

Table 2. Demographics and Baseline Characteristics

Category	**Placebo N=81**	**Perampanel N=81**	**Total N=162**
Age (year)			
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
<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)

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Category	Placebo N=81	Perampanel N=81	Total N=162
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)
PGTC Seizure Frequency per 28 Days			
Mean (SD)	3.17 (2.000)	3.50 (2.620)	3.33 (2.329)
Median	2.50	2.55	2.50
Min, Max	1.0, 11.7	1.4, 18.5	1.0, 18.5

Source: Table 6 and 7 of the CSR, and the reviewer.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

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 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 3. PGTC Seizure 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: Table 10 of the CSR, confirmed by the reviewer.

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Sensitivity Analyses for the Primary Endpoint

The findings of the primary analysis were supported by sensitivity analyses using different analysis populations (Per Protocol Analysis Set and completer set) and difference study period (Maintenance).

The reviewer conducted an additional sensitivity analysis on the ITT population using non-parametric ANCOVA. The result was consistent with the primary analysis.

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, this reviewer conducted an analysis in which all available seizure data were used. The result was almost identical with that of the primary analysis. The estimated median treatment difference from placebo was -29.01% (P<0.0001).

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

3.2.4.2 Analyses of Secondary Endpoints

Table 4 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 4. PGTC 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: Table 11 of the CSR, confirmed by the reviewer.

The findings of the primary analysis were supported by sensitivity analyses using different analysis populations (Per Protocol Analysis Set and completer set) and difference study period (Titration and Maintenance combined). This reviewer conducted a worst-case analysis in which discontinuation in the perampanel group were considered as non-responders. The result still favored the perampanel group (P=0.0215).

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3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The analysis results for the primary endpoint by demographic subgroups (with at least one subject in each treatment group) are in Table 5. The treatment effect was generally consistent across the subgroups.

Table 5. Percent Change in PGTC Seizure Frequency by Subgroups

	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

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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: FDA reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The study completion rates were comparable between the two groups and the diary compliance was high. The impact of dropouts and missing data on the efficacy evaluation was minimal.

5.2 Collective Evidence

The results of both the primary efficacy endpoint and the key secondary endpoint demonstrated that perampanel reduced the occurrence of PGTC seizures. The median percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to baseline was statistically significantly larger for perampanel (-76.47%) than for placebo (-38.38%), with an estimated median treatment difference of -30.81% ($P<0.0001$). The 50% PGTC responder rate during the Maintenance period was statistically significantly higher in the perampanel group (64.2%) than in the placebo group (39.5%) ($P=0.0019$).

The findings of the primary efficacy analyses were supported by sensitivity analyses including worst-case type of analyses. The effect of perampanel was generally consistent across demographic subgroups.

5.3 Conclusions and Recommendations

The data overall provided evidence to support for the efficacy of perampanel as adjunctive treatment in adult and adolescent subjects with previously inadequately controlled PGTC seizures.

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/s/

XIANG LING
04/13/2015

KUN JIN
04/13/2015
I concur with the review.

KOOROS MAHJOOB
04/13/2015
the review and dicussed my views with the revewer. I concur with the review