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/Serial Number:	NDA202-834/0011
Drug Name:	Perampanel Tablets
Indication(s):	Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Applicant:	Eisai Inc
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Keywords:	Perampanel, Refractory partial seizures, Epilepsy, ITT analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The three clinical studies 304, 305 and 306 support that perampanel 4, 8 and 12 mg are effective in reducing seizure frequencies in subjects with refractory partial seizures. However, the results of the efficacy in Study 304 are not consistent because the statistical significance in the test of efficacy varies, depending on the patient population included in the analysis, and the change of patient population was made after the study completed. Therefore Study 304 may be used as supportive for efficacy.

1.2 Brief Overview of Clinical Studies

This NDA includes three randomized, double-blind, parallel-group, placebo-controlled phase III studies (304, 305, and 306) to support the safety and efficacy of perampanel in the treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older. The studies are described as follows (Table 1):

Table 1 List of Study Included in Analysis

Study	Sample Size	Phase and Design	Treatment Period	Follow-up Period	# of Subjects Per Arm	Study Population
304	390	Randomized, double-blind, placebo-controlled, parallel-group, Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 122 8 mg: 133 12 mg: 135	epilepsy
305	389	Randomized, double-blind, placebo-controlled, parallel-group, Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 138 8 mg: 130 12 mg: 121	epilepsy
306	712	Randomized, double-blind, placebo-controlled, parallel-group,Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 187 2 mg: 180 4 mg: 174 8 mg: 171	epilepsy

1.3 Statistical Issues and Findings

Use of the full analysis set for primary analysis is important in clinical trials. The full analysis set includes all randomized subjects by intention-to-treat principle, and tends to avoid over-optimistic estimates of efficacy resulting from the analysis set that excludes subjects with condition. In the three studies of this NDA, the ITT analysis set was pre-specified for the primary analysis in the protocol and SAP. The ITT analysis set excludes subjects who did not have at least two weeks of seizure frequency data from the pre-randomization phase and from the double-blind Phase. In reviewing the sponsor's protocol and SAP, the agency recommended that the full ITT analysis set should be used for the primary analysis , but the sponsor did not take the agency's recommendation into consideration until later time in the trial prior to data un-blinded for Study 305, and when Study 304 and Study 306 have completed.

Pre-specification of the analysis is also necessary to avoid any potential bias in interpretation of study result. An amendment was made to Study 304 and Study 306 when both studies have completed. The analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis when the originally planned ITT analysis set was used, but would win only when the full ITT analysis set was used ,

2. INTRODUCTION

2.1 Overview

Epilepsies are among the most common neurologic disorders affecting individuals of all ages. Over the past 15 years, several antiepileptic drugs (AEDs) have been developed with the objective of improving efficacy, tolerability, and ease of use when compared with classic currently-used AEDs. While these newer medications are efficacious and relatively safe, none have completely met the treatment needs of all patients with epilepsy. Perampanel is an orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that has been developed as adjunctive treatment for patients with partial-onset seizures.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\cdsesub1\EVSPROD\NDA202834\0011 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

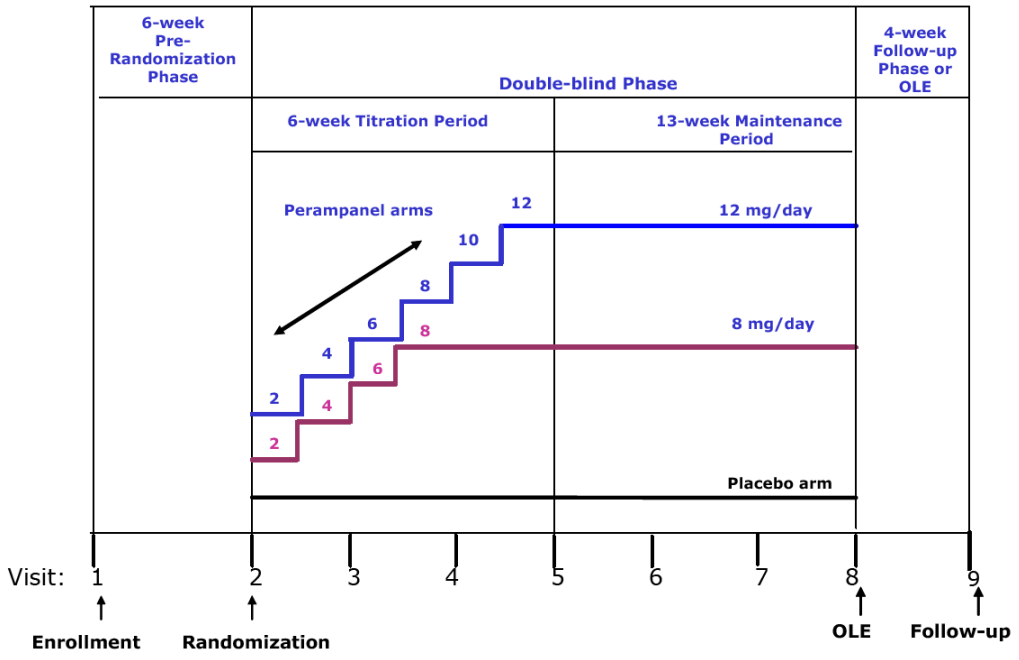
The primary objective of the studies was to evaluate the efficacy of two or three doses of perampanel (8 and 12 mg for Study 304 & 305; 2, 4 and 8 mg for Study 306) given as adjunctive therapy in subjects with refractory partial seizures.

3.1.2 Study Design

The studies were double-blind, placebo-controlled, dose-escalation, parallel-group, multiple-region studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures. The studies include three phases: Prerandomization, Double-blind (including titration and maintenance periods) and Follow-up. The detail of the study design is described as follows (Figure 1).

Figure 1 Study Design

Study 304 and 305



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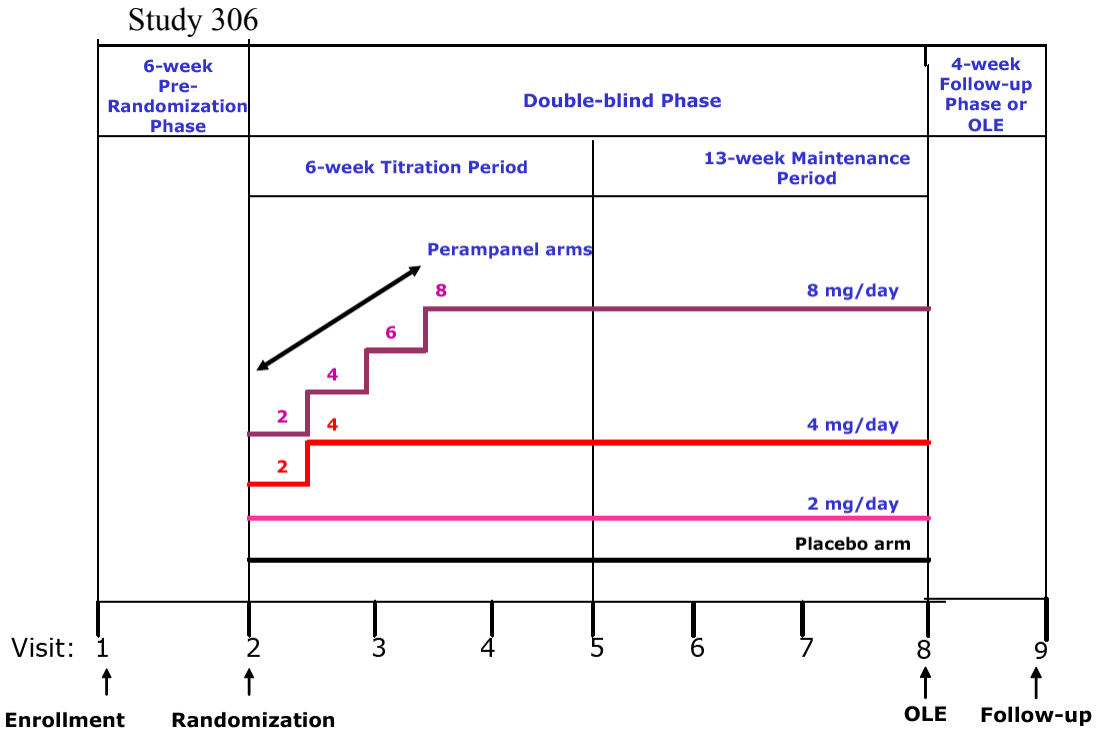

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(Source: Sponsor's Figure 9.1)

3.1.3 Efficacy Measures

1) Primary Efficacy Endpoint

Percent change in seizure frequency: The primary efficacy measure was the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomization Phase in the ITT Analysis set using LOCF imputation. Primary analysis period is the Maintenance Period **originally planned for all three studies**, **and The Double Blind Period amended later for Study 305.** Seizure frequency will be based on the number of seizures per 28 days, calculated as (the number of seizures over the time interval multiplied by 28) and divided by the number of days in the interval.

2) Secondary Efficacy Endpoints

- Percent change in the frequency of complex partial plus secondarily generalized seizures
- Responder rate: Responder rate is the key secondary endpoint for the non-EMEA registrants
- Dose-response analysis

3.1.4 Statistical Analysis Methodology

1) 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 analysis of covariance (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. Hodges−Lehmann estimator and 95% confidence interval (CI) for the estimator were calculated.

2) Responder rate: An analysis of subjects who experience a 50% or greater reduction in seizure frequency in the Maintenance period of the double-blind phase relative to the pre-randomization phase will be conducted based on Cochran-Mantel-Haenszel (CMH) test adjusting for pooled countries.

3) Handling of missing data, drop-outs, and outliers: The primary analysis of seizure frequency will be based on the Maintenance Period using LOCF imputation. If the overall duration of the Maintenance Period is less than 8 weeks, the diary data from the last 8 weeks during the treatment phase (Titration Period + Maintenance Period) will be used to calculate the seizure frequency per 28 days for Maintenance-LOCF. When the proportion of randomized subjects with less than 2 weeks of Double-blind Phase seizure data is greater than 10%, the endpoint seizure frequency of such subjects will be calculated based on their last 2 weeks of seizure data (including some days before randomization). When the proportion of randomized subjects with less than 2 weeks of Double-blind Phase seizure data is less than or equal to 10%, the Double-blind Phase seizure frequencies of such subject will be set to missing.

4) Multiple Comparisons/Multiplicity: For primary efficacy endpoint, a closed testing procedure will be employed to control family wise type-I error rate. For Study 304 & 305, the test starts from the lower dose, first the 8 mg treatment group will be compared with the placebo at the two-sided alpha level of 0.05. If this comparison demonstrates superiority then the 8 mg treatment group will be declared efficacious; 12 mg treatment group will then be compared to the placebo at the two-sided alpha level of 0.05.

   For Study 306, the test starts from the higher dose. First, the 8 mg treatment group was compared with placebo at the two-sided alpha level of 0.05. If this comparison demonstrated superiority, then the 8 mg treatment group will be declared efficacious. The 4 mg treatment group was then compared with placebo at the two-sided alpha level of 0.05. If both the 8 and 4 mg treatment groups were statistically superior to placebo at the two-sided alpha level of 0.05, the 2 mg treatment group was then compared with placebo at the two-sided alpha level of 0.05 to test for superiority.

5) Pooling of centers: Data from the centers in the same country will be pooled together for analysis purposes. Each of these countries should have at least 12 subjects. If there

are countries with <12 subjects then the countries will be sorted in descending order by the number of subjects. Starting from the smallest, countries will be pooled until the criteria of 12 subjects is fulfilled or there is no country of size <12 left to be pooled. If there is no country of size <12 left to be pooled but the current country is of size <12 then the current country will be pooled with the next country in the order.

3.15 Patient Disposition, Demographic and Baseline Characteristics

Tables 2-4 summarize patient disposition, demographic and baseline characteristics in the three studies.

Table 2 Patient disposition, demographic and baseline characteristics, Full ITT, Study 304

		Perampanel			
Category	Placebo (N=121)	8 mg (N=133)	12 mg (N=133)	Total (N=266)	Combined Total (N=387)
Age(Year)[a]					
n	121	133	133	266	387
Mean (SD)	35.6 (14.67)	35.8 (14.21)	36.7 (14.69)	36.3 (14.43)	36.1 (14.49)
Median	34.0	36.0	36.0	36.0	35.0
Min, Max	12, 73	12, 68	14, 77	12, 77	12, 77
Age Group, n (%)					
<18	14 (11.6)	15 (11.3)	10 (7.5)	25 (9.4)	39 (10.1)
18-64	102 (84.3)	116 (87.2)	118 (88.7)	234 (88.0)	336 (86.8)
>64	5 (4.1)	2 (1.5)	5 (3.8)	7 (2.6)	12 (3.1)
Sex, n (%)					
Male	54 (44.6)	65 (48.9)	69 (51.9)	134 (50.4)	188 (48.6)
Female	67 (55.4)	68 (51.1)	64 (48.1)	132 (49.6)	199 (51.4)
Race, n (%)					
White	103 (85.1)	115 (86.5)	115 (86.5)	230 (86.5)	333 (86.0)
Black or African American	13 (10.7)	6 (4.5)	8 (6.0)	14 (5.3)	27 (7.0)
Asian	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Japanese	0	0	0	0	0
Chinese	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
American Indian or Alaska Native	0	4 (3.0)	2 (1.5)	6 (2.3)	6 (1.6)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	5 (4.1)	6 (4.5)	6 (4.5)	12 (4.5)	17 (4.4)
Ethnicity, n (%)					
Hispanic or Latino	53 (43.8)	66 (49.6)	57 (42.9)	123 (46.2)	176 (45.5)
Not Hispanic or Latino	68 (56.2)	67 (50.4)	76 (57.1)	143 (53.8)	211 (54.5)
Weight(kg)					
n	121	132	133	265	386
Mean (SD)	72.55 (20.535)	71.07 (17.953)	73.87 (18.717)	72.47 (18.360)	72.50 (19.041)
Median	68.60	71.95	69.70	71.00	70.00
Min, Max	33.1, 141.2	37.8, 116.2	40.0, 136.3	37.8, 136.3	33.1, 141.2
Height(cm)					
n	116	131	133	264	380
Mean (SD)	164.08 (11.209)	165.63 (9.024)	167.25 (9.976)	166.45 (9.532)	165.72 (10.118)
Median	164.10	165.60	167.60	167.00	165.10
Min, Max	139.0, 193.0	143.0, 188.0	146.0, 193.0	143.0, 193.0	139.0, 193.0
BMI(kg/m2)[b]					
n	116	130	133	263	379
Mean (SD)	26.72 (6.169)	25.87 (5.507)	26.38 (6.190)	26.12 (5.857)	26.30 (5.952)
Median	25.33	25.35	25.25	25.25	25.27
Min, Max	16.7, 50.5	15.1, 45.3	17.6, 43.9	15.1, 45.3	15.1, 50.5
Baseline of seizure frequency					
N	121	133	133	266	387
Mean (SD)	26.76 (32.23)	35.45 (94.04)	41.38 (109.55)	38.41 (101.94)	34.77 (86.52)
Median	13.66	14.34	12.00	12.98	13.30
Min, Max	3.3, 227.4	2.4, 1030.8	2.9, 1083.1	2.4, 1083.1	2.4, 1083.1

(Source: Sponsor's Table 14.1.10, confirmed by the reviewer's analysis)

Table 3 Patient disposition, demographic and baseline characteristics, Full ITT, Study 305

Category	Placebo (N=136)	Perampanel 8 mg (N=129)	Perampanel 12 mg (N=121)	Perampanel Total (N=250)	Combined Total (N=386)
Age(Year)[a]					
n	136	129	121	250	386
Mean (SD)	34.4 (13.62)	36.7 (14.35)	35.5 (14.12)	36.1 (14.22)	35.5 (14.02)
Median	35.0	37.0	35.0	35.5	35.0
Min, Max	12, 76	12, 72	12, 74	12, 74	12, 76
Age Group, n (%)					
<18	17 (12.5)	17 (13.2)	10 (8.3)	27 (10.8)	44 (11.4)
18-64	118 (86.8)	109 (84.5)	109 (90.1)	218 (87.2)	336 (87.0)
>64	1 (<1)	3 (2.3)	2 (1.7)	5 (2.0)	6 (1.6)
Sex, n (%)					
Male	71 (52.2)	65 (50.4)	50 (41.3)	115 (46.0)	186 (48.2)
Female	65 (47.8)	64 (49.6)	71 (58.7)	135 (54.0)	200 (51.8)
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)
Japanese	0	0	0	0	0
Chinese	0	0	0	0	0
American Indian or Alaska Native	1 (<1)	0	0	0	1 (<1)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	7 (5.1)	6 (4.7)	4 (3.3)	10 (4.0)	17 (4.4)
Ethnicity, n (%)					
Hispanic or Latino	13 (9.6)	9 (7.0)	6 (5.0)	15 (6.0)	28 (7.3)
Not Hispanic or Latino	123 (90.4)	120 (93.0)	115 (95.0)	235 (94.0)	358 (92.7)
Weight(kg)					
n	136	129	121	250	386
Mean (SD)	71.64 (17.589)	72.00 (19.011)	71.90 (18.693)	71.95 (18.820)	71.84 (18.373)
Median	69.25	72.30	67.00	69.80	69.55
Min, Max	40.0, 128.0	34.0, 136.3	34.7, 130.5	34.0, 136.3	34.0, 136.3
Height(cm)					
n	136	128	118	246	382
Mean (SD)	168.26 (9.777)	167.43 (9.235)	166.26 (9.868)	166.87 (9.543)	167.36 (9.637)
Median	168.00	167.00	167.00	167.00	167.60
Min, Max	139.5, 193.0	142.0, 189.2	140.5, 193.5	140.5, 193.5	139.5, 193.5
BMI(kg/m2)[b]					
n	136	128	118	246	382
Mean (SD)	25.17 (5.223)	25.57 (6.116)	25.70 (5.963)	25.63 (6.031)	25.47 (5.754)
Median	24.27	24.82	24.92	24.86	24.73
Min, Max	15.6, 44.8	15.4, 44.5	15.9, 45.7	15.4, 45.7	15.4, 45.7
Baseline of seizure frequency					
N	136	129	121	250	386
Mean (SD)	32.03 (52.72)	37.59 (80.94)	42.29 (94.79)	39.86 (87.77)	37.11 (77.27)
Median	11.79	13.02	13.69	13.67	12.95
Min, Max	3.4, 358.4	3.3, 652.2	1.4, 598.4	1.4, 652.2	1.4, 652.2

(Source: Sponsor's Table 14.1.5.2, confirmed by the reviewer's analysis)

Table 4 Patient disposition, demographic and baseline characteristics, Full ITT, Study 306

		Perampanel				
Category	Placebo (N=184)	2 mg (N=180)	4 mg (N=172)	8 mg (N=169)	Total (N=521)	Combined Total (N=705)
Age(Year)[a]						
n	184	180	172	169	521	705
Mean (SD)	33.4 (12.58)	33.8 (13.62)	33.6 (12.19)	34.6 (12.77)	34.0 (12.87)	33.8 (12.79)
Median	31.0	32.0	32.0	33.0	32.0	32.0
Min, Max	12, 66	13, 72	12, 68	12, 69	12, 72	12, 72
Age Group, n (%)						
<18	14 (7.6)	21 (11.7)	13 (7.6)	12 (7.1)	46 (8.8)	60 (8.5)
18-64	168 (91.3)	156 (86.7)	158 (91.9)	153 (90.5)	467 (89.6)	635 (90.1)
>64	2 (1.1)	3 (1.7)	1 (<1)	4 (2.4)	8 (1.5)	10 (1.4)
Sex, n (%)						
Male	95 (51.6)	85 (47.2)	88 (51.2)	77 (45.6)	250 (48.0)	345 (48.9)
Female	89 (48.4)	95 (52.8)	84 (48.8)	92 (54.4)	271 (52.0)	360 (51.1)
Race, n (%)						
White	119 (64.7)	119 (66.1)	105 (61.0)	116 (68.6)	340 (65.3)	459 (65.1)
Black or African American	0	0	0	0	0	0
Asian	33 (17.9)	35 (19.4)	37 (21.5)	28 (16.6)	100 (19.2)	133 (18.9)
Japanese	0	0	0	0	0	0
Chinese	31 (16.8)	25 (13.9)	29 (16.9)	25 (14.8)	79 (15.2)	110 (15.6)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Other	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	3 (<1)
Ethnicity, n (%)						
Hispanic or Latino	10 (5.4)	9 (5.0)	9 (5.2)	10 (5.9)	28 (5.4)	38 (5.4)
Not Hispanic or Latino	174 (94.6)	171 (95.0)	163 (94.8)	159 (94.1)	493 (94.6)	667 (94.6)
Weight(kg)						
n	184	180	172	169	521	705
Mean (SD)	67.54 (16.007)	65.37 (16.173)	69.49 (17.210)	68.47 (16.284)	67.73 (16.621)	67.68 (16.452)
Median	67.00	64.10	68.65	67.00	67.00	67.00
Min, Max	30.6, 126.7	35.0, 114.0	23.3, 132.5	36.0, 114.0	23.3, 132.5	23.3, 132.5
Height(cm)						
n	184	179	172	169	520	704
Mean (SD)	167.65 (10.076)	166.11 (9.208)	167.94 (11.185)	167.22 (10.188)	167.08 (10.221)	167.23 (10.179)
Median	168.00	165.00	167.25	167.00	167.00	167.00
Min, Max	136.0, 193.0	144.5, 190.5	126.0, 198.0	142.0, 193.0	126.0, 198.0	126.0, 198.0
BMI(kg/m2)[b]						
n	184	179	172	169	520	704
Mean (SD)	23.89 (4.754)	23.51 (4.584)	24.46 (4.745)	24.36 (4.896)	24.10 (4.751)	24.05 (4.749)
Median	23.06	23.23	23.82	23.93	23.71	23.52
Min, Max	14.0, 43.2	16.4, 41.7	12.1, 39.6	15.7, 39.0	12.1, 41.7	12.1, 43.2
Baseline of seizure frequency						
N	184	180	172	169	521	705
Mean (SD)	23.94 (50.54)	31.20 (55.42)	62.56 (354.87)	32.61 (73.13)	42.01 (210.73)	37.30 (183.11)
Median	9.33	10.12	10.02	10.93	10.24	9.84
Min, Max	3.3, 569.1	3.2, 429.6	2.9, 4503.9	3.4, 723.2	2.9, 4503.9	2.9, 4503.9

(Source: Sponsor's Table 14.1.10, confirmed by the reviewer's analysis)

3.16 Sponsor's Primary Efficacy Results

Percent Change in Seizure Frequency:

1) The median changes in both doses of perampanel are statistically significant larger comparing to placebo in both Study 304 and Study 305 (Study 304: p=0.0261, and p=0.0184 for 8 mg and 12 mg perampanel, respectively; Study 305: p=0.0008 and p=0.0105 for 8 mg and 12 mg perampanel, respectively) (Tables 5, 6).

Table 5 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full 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	0.0158

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

Table 6 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full 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)		-19.10 (-29.17, -8.45)	-13.69 (-25.20, -2.26)
P-value		0.0008	0.0105

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

2) In Study 306, the median changes in the two higher doses of perampanel are statistically significant larger comparing to placebo ($p=0.0026$, $p<0.0001$ for 4 mg and 8 mg perampanel, respectively) (Table 7).

Table 7 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT), Study 306

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	184	180	172	169
Median	-10.69	-13.63	-23.33	-30.80
Median Difference to Placebo (95% CI)		-4.36 (-14.09, 5.22)	-13.71 (-23.31, -4.50)	-20.13 (-29.66, -10.43)
P-value		0.42	0.0026	<0.0001

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

3.17 Sponsor's Secondary Efficacy Results

1) Responder Rate

In Study 304, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in both dose groups compared to placebo (26.4%, 37.6%, and 36.1% for placebo, 8 mg, 12 mg, respectively), but the difference in responder rate between perampanel and placebo was not statistically significant (Table 8).

Table 8 Responder Analysis (Full ITT, Maintenance-LOCF), Study 304

		Perampanel	
Analysis Window Responder	Placebo (N=121) n (%)	8 mg (N=133) n (%)	12 mg (N=133) n (%)
Maintenance-LOCF			
Yes	32 (26.4)	50 (37.6)	48 (36.1)
No	89 (73.6)	83 (62.4)	85 (63.9)
Total	121 (100)	133 (100)	133 (100)
p-value[a]			
Compared with Placebo		0.0760	0.0914

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

In Study 305, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in both dose groups compared to placebo (14.7%, 33.3%, and 33.9% for placebo, 8 mg, 12 mg perampanel , respectively), the difference in responder rate between perampanel and placebo was statistically significant (Table 9).

Table 9 Responder Analysis (Full ITT, Maintenance-LOCF), Study 305

		Perampanel	
Analysis Window Responder	Placebo (N=136) n (%)	8 mg (N=129) n (%)	12 mg (N=121) n (%)
Maintenance-LOCF			
Yes	20 (14.7)	43 (33.3)	41 (33.9)
No	116 (85.3)	86 (66.7)	80 (66.1)
Total	136 (100)	129 (100)	121 (100)
p-value[a]			
Compared with Placebo		0.0018	0.0006

(Source: Sponsor's Table 11.6, confirmed by the reviewer's analysis)

In Study 306, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in the two higher dose groups compared to placebo (17.9%, 28.5%, and 34.9% for placebo, 4 mg, 8 mg perampanel, respectively), the difference in responder rate between perampanel and placebo was statistically significant (Table 10).

Table 10 Responder Analysis (Full ITT, Maintenance-LOCF), Study 306

Analysis Window Responder	Placebo (N=184) n (%)	Perampanel 2 mg (N=180) n (%)	Perampanel 4 mg (N=172) n (%)	Perampanel 8 mg (N=169) n (%)
Maintenance-LOCF				
Yes	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
No	151 (82.1)	143 (79.4)	123 (71.5)	110 (65.1)
Total	184 (100)	180 (100)	172 (100)	169 (100)
p-value[a]				
Compared with Placebo		0.4863	0.0132	0.0003

(Source: Sponsor's Table 11.6, confirmed by the reviewer's analysis)

2) Percent Change in Frequency of Complex Partial Plus Secondarily Generalized Seizures

Complex partial plus secondarily generalized seizures include complex partial seizures and complex partial with secondary generalization seizures.

In Study 304 and Study 3.5, the median changes in both doses of perampanel are statistically significant larger comparing to placebo (Study 304: p=0.002, and p=0.0081 for 8 mg and 12 mg perampanel, respectively; Study 305: p=0.0007, and p=0.0045 for 8 mg and 12 mg perampanel, respectively) (Tables 11-12).

In Study 306, the median changes in the two higher doses of perampanel are statistically significant larger comparing to placebo (p=0.0070, p=0.0005 for 4 mg and 8 mg perampanel, respectively) (Table 13).

Table 11 Percent Change in Seizure Frequency per 28 Days -Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 304

Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	110	120	120
Median	-17.88	-33.03	-33.06
Median Difference to Placebo (95% CI)		-20.37 (-33.16, -7.74)	-17.90 (-30.31, -4.67)
P-value		0.0020	0.0081

(Source: Sponsor's Table 11.9, confirmed by the reviewer's analysis)

Table 12 Percent Change in Seizure Frequency per 28 Days –Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 305

Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	126	119	113
Median	-8.05	-32.72	-21.89
Median Difference to Placebo (95% CI)		-23.07 (-34.80, -10.55)	-17.45 (-29.27, -5.70)
P-value		0.0007	0.0045

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

Table 13 Percent Change in Seizure Frequency per 28 Days –Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 306

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	169	167	157	154
Median	-17.63	-20.50	-31.18	-38.69
Median Difference to Placebo (95% CI)		-3.26 (-13.69, 7.40)	-14.40 (-25.08, -3.50)	-19.32 (-29.79, -8.63
P-value		0.6506	0.0070	0.0005

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

3.18 Reviewer's Results

1) The reviewer verified the sponsor's primary and secondary efficacy analyses and concurred with their results.

2) An amendment was made to Study 305 in a later time of the trial prior to data un-blinded, the analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. This change was also made to Study 304 and Study 306 when both studies have completed. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis based on the originally planned ITT analysis set, but would win only when the full ITT analysis set was used (Tables 14, 15 & 16).

Table 14 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline(Full ITT/ITT Analysis Set), Study 304

	Full ITT Analysis Set			ITT Analysis Set		
Statistic	Placebo	Perampanel		Placebo	Perampanel	
		8 mg	12 mg		8 mg	12 mg
n	121	133	133	119	132	130
Median	-20.95	-26.34	-34.49	-22.86	-32.13	-39.48
Median Difference to Placebo (95% CI)		-13.53 (-26.17, -1.94)	-14.20 (-25.03, -2.73)		-11.67 (-23.69, 1.25	-12.64 (-24.17, -1.13)
P-Value		0.0261	0.0158		0.0812	0.0304

(Source: Sponsor's Table 11.5 & Table 14.2.1.1.1.1)

Table 15 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT/ITT Analysis Set), Study 305

	Full ITT Analysis Set			ITT Analysis Set		
Statistic	Placebo	Perampanel		Placebo	Perampanel	
		8 mg	12 mg		8 mg	12 mg
n	136	129	121	135	126	118
Median	-9.72	-30.52	-17.57	-10.44	-31.32	-17.66
Median Difference to Placebo (95% CI)		-19.10 (-29.17, -8.45)	-13.69 (-25.20, -2.26)		-19.49 (-29.70, -9.05)	-13.38 (-24.83, -2.06)
P-Value		0.0008	0.0105		0.0007	0.0142

(Source: Sponsor's Table 11.5 & Table Table 14.2.1.1.7.1)

Table 16 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT/ITT Analysis Set), Study 306

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
Full ITT Analysis Set				
n	184	180	172	169
Median	-10.69	-13.63	-23.33	-30.80
Median Difference to Placebo (95% CI)		-4.36 (-14.09, 5.22)	-13.71 (-23.31, -4.50)	-20.13 (-29.66, -10.43)
P-value		0.42	0.0026	<0.0001
ITT Analysis Set				
n	182	177	168	166
Median	-10.11	-14.13	-23.99	-31.34
Median Difference to Placebo (95% CI)		-5.88 (-15.59, 3.78	-14.83 (-24.42, -5.55)	-20.78 (-30.33, -11.00
P-value		0.26	0.0008	<0.0001

(Source: Sponsor's Table 11.5 & Table 14.2.1.1.1.1)

3) The reviewer compared and checked the discrepancy between the two analysis sets. According to the original protocol, six patients who did not have at least 2 weeks of seizure frequency data from the pre-randomization phase and at least 2 weeks of seizure frequency data from the double-blind Phase were excluded from the Full ITT analysis set. The six patients discontinued the study due to adverse event(s) in a short time after receiving treatments (1-13 days). There are no special patterns observed, in terms of treatment received and the LOCF value of the primary endpoint. Two patients were in the placebo group, and 4 patients in the 12 mg parampanel group. The LOCF values of the primary endpoint range from 38.46% to -100% (Table 17).

   The discrepancy in the analysis sets seems to have an impact on the efficacy result. It maybe due to a large variation in the imputed LOCF values of the primary endpoint since these patients withdraw early from the study.

Table 17 Patients Excluded from the Full ITT Analysis Set

Subject	Treatment Group	Days on Treatment	LOCF Value
1	12 mg	4	-100.00%
2	Placebo	7	-100.00%
3	12 mg	11	43.66%
4	12 mg	3	-8.40%
5	Placebo	13	38.46%
6	12 mg	1	-100.00%

(Source: The reviewer's analysis)

3.19 Conclusions

Both analysis sets yield a consistent efficacy results in Study 305 and Study 306, but not in Study304. In Study 304, a statistically significant result of efficacy is shown only if the full analysis set is used, and use of the full analysis set for the primary analysis was not planned in the protocol and SAP.

3.2 Evaluation of Safety

Please refer to Dr. Rusinowitz's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup analysis—age group

It appears that the efficacy of parampanel is in a right direction across all doses in subjects aged 64 years old or younger in all three studies (Table 18).

Table 18 Subgroup Analysis of Primary endpoint by Age Group, (Full ITT)

Age (years)	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
<18	14	-15.90					15	-56.45	10	-35.56
18-64	102	-21.68					116	-25.38	118	-34.71
>64	5	-1.8					2	13.6	5	-12.49
Study 305										
<18	17	-22.86					17	-32.72	10	-43.87
18-64	118	-7.13					119	-26.64	119	-17.28
>64	1	-8.77					3	1.73	2	-40.60
Study 306										
<18	14	4.57	21	12.77	13	-23.91	12	-34.61		
18-64	166	-10.36	153	-16.55	154	-24.11	150	-30.62		
>64	2	-59.45	3	-66.57	1	19.31	4	-28.37		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.2 Subgroup analysis—sex

The efficacy of parampanel is also in a right direction in both genders across all doses in all three studies (Table 19).

Table 19 Subgroup Analysis of Primary endpoint by Sex, (Full ITT)

Sex	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
Male	54	-21.97					65	-21.82	69	-30.11
Female	67	-15.90					68	-39.91	64	-38.11
Study 305										
Male	71	-11.85					65	-30.52	50	-14.64
Female	65	-8.77					64	-30.15	71	-17.57
Study 306										
Male	95	-10.94	83	-16.55	85	-19.02	77	-21.43		
Female	87	-8.54	94	-12.43	83	-26.14	89	-37.93		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.3 Subgroup analysis—race

The efficacy of parampanel is shown in a right direction in both ethnicity groups across all doses in all three studies (Table 20).

Table 20 Subgroup Analysis of Primary endpoint by Race, (Full ITT)

Race	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
White	103	-21.74					115	-25.25	115	-33.51
Non-white	18	-15.63					18	-32.04	18	-42.16
Study 305										
White	115	-8.77					107	-26.64	100	-20.16
Non-white	21	-29.55					22	-52.30	21	-21.64
Study 306										
White	119	-11.11	116	-11.63	103	-23.91	115	-26.20		
Non-white	63	-7.69	61	-19.05	65	-24.14	51	-38.89		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.4 Subgroup analysis—region

The efficacy of parampanel is also shown in a right direction in all regions across all doses in Study 304 and Study 305. In Study 306, the efficacy of parampanel seems to be inconsistent across doses in the Russia region, it may be due to a small sample size in this region (Table 21).

Table 21 Subgroup Analysis of Primary endpoint by Region, (Full ITT)

Region	Placebo		2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
North America	73	-11.34					74	-27.63	80	-36.91
USA	66	-9.52					64	-25.38	72	-35.22
Central & South America	48	-26.18					59	-24.88	53	-20.73
Study 305										
Europe	84	-2.11					75	-20.04	70	-14.88
USA	33	-23.31					31	-41.64	27	-21.64
India	10	-33.79					14	-45.42	14	-30.66
Russia	9	-5.63					9	-23.68	10	-31.02

Study 306										
Europe	103	-12.66	101	-13.72	96	-25.24	100	-34.89		
Asia	62	-8.12	60	-19.78	60	-23.45	50	-36.76		
Russia	17	-3.28	16	14.61	12	-5.83	16	0.46		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1 & Reviewer's Analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Use of the full analysis set for primary analysis is important in clinical trials. The full analysis set includes all randomized subjects by intention-to-treat principle, and tends to avoid over-optimistic estimates of efficacy resulting from the analysis set that excludes subjects with condition. In the three studies of this NDA, the ITT analysis set was pre-specified for the primary analysis in the protocol and SAP. The ITT analysis set excludes subjects who did not have at least two weeks of seizure frequency data from the pre-randomization phase and from the double-blind Phase. In reviewing the sponsor's protocol and SAP, the agency recommended that the full ITT analysis set should be used for the primary analysis , but the sponsor did not take the agency's recommendation into consideration until later time in the trial prior to data un-blinded in Study 305, and when both Study 304 and Study 306 have completed.

Pre-specification of the analysis is also necessary to avoid any potential bias in interpretation of study result. An amendment was made to Study 304 and Study 306 when both studies have completed, the analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis based on the originally planned ITT analysis set, but would win only when the full ITT analysis set was used.

5.2 Conclusions and Recommendations

The three clinical studies 304, 305 and 306 support that perampanel 4, 8 and 12 mg are effective in reducing seizure frequencies in subjects with refractory partial seizures. However, the results of the efficacy in Study 304 are not consistent because the statistical significance in the test of efficacy varies, depending on the patient population included in the analysis, and the change of patient population was made after the study completed. Therefore Study 304 may be used as supportive for efficacy.

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/s/

QUQUAN LIU
08/30/2012

KUN JIN
08/30/2012
I concur with the review.

HSIEN MING J HUNG
08/30/2012