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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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

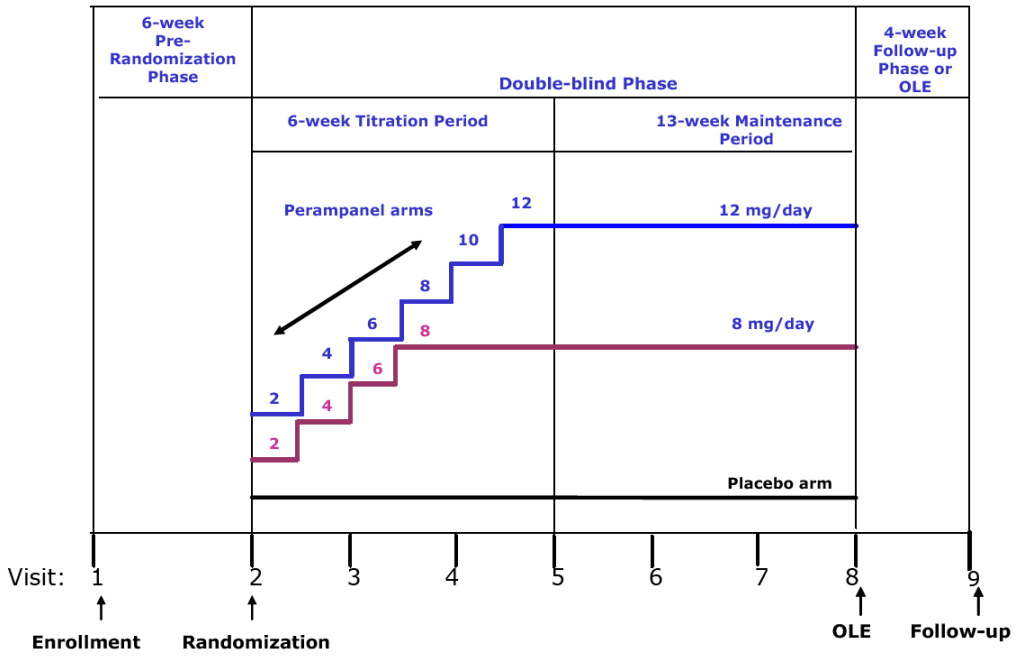
The primary objective of the studies was to evaluate the efficacy of two or three doses of perampanel (8 and 12 mg for Study 304 & 305; 2, 4 and 8 mg for Study 306) given as adjunctive therapy in subjects with refractory partial seizures.

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



OLE = open-label extension

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/

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08/30/2012

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I concur with the review.

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08/30/2012