2 SYNOPSIS

Sponsor: **Eisai Medical Research, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: **perampanel**	**Volume:**	
Name of Active Ingredient: **2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile**	**Page:**	

Study Title:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Explore the Safety and Tolerability of Doses of E2007 up to a Maximum of 12 mg in Patients with Refractory Partial Seizures

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): see Appendix 16.1.11

Studied Period:

first subject enrolled: 13 Mar 2007
last subject completed: 15 Jan 2008

Phase of Development: 2b

Objectives:

Primary

The primary objective of this study was to determine the safety and tolerability of doses up to a maximum of 12 mg per day of E2007 (perampanel) in patients with refractory partial seizures who were taking inducing and noninducing anti-epileptic drugs (AEDs).

Secondary

- To investigate the efficacy of perampanel for the treatment of partial seizures; and
- To explore the relationship between perampanel plasma concentrations and safety and efficacy measurements.

Exploratory

- To determine the proportion of responders at the maximum tolerated dose (MTD) in the Maintenance Phase.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group study. Subjects were initially stratified (inducers vs non-inducers of the cytochrome P450 3A4 isoenzyme) according to their concomitant AEDs, with the aim to recruit approximately 24 subjects to each stratum. Following stratification, subjects were then randomized to 1 of 2 double-blind treatment groups in a 3:1 ratio (perampanel to placebo) such that, within each stratum, approximately 18 subjects were to receive perampanel and approximately 6 subjects were to receive placebo. All subjects were to receive treatment for a total of 16 weeks (Days 1 to 112). Induced subjects were to be treated with 2 to 3 (maximum) marketed and approved anti-epileptic inducer medications such as: carbamazepine, phenytoin, phenobarbital, or primidone (revised per Amendment A). Non-induced subjects were to be treated with 2 to 3 (maximum) marketed and approved anti-epileptic noninducer medications such as: topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or levetiracetam, and none of the drugs in the inducer group (revised per Amendment A). Subjects on multiple AEDs were to be considered as induced if at least 1 concomitant medication was an inducer. The study was to consist of the following phases:

- Baseline Phase (4 weeks, Days –28 to –1): prospective ascertainment of seizure frequency based on the subject's diary. To be enrolled into the study, a 4-week retrospective baseline using the subject's diary was to be evaluated.

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- Titration Phase (12 weeks, Days 1 to 84): During the dose-titration period, study drug dosing in the perampanel group was to be started at 2 mg once daily and titrated up to 12 mg. Titrations were to be made at 2-week intervals on the basis of individual tolerability and in 2-mg incremental steps (ie, subjects were to be titrated from 2 mg to 4 mg to 6 mg to 8 mg to 10 mg to 12 mg). Subjects were to be instructed to take the study drug in the evening with food, except on Visit Days 1, 15, 29, 43, 57, 71, and 85. On only those days, subjects were to receive their study drug with food during their clinic visit. At each titration step, the investigator was to review all data available for each subject. The dose was only to be increased if, in the opinion of the investigator and with the agreement of the subject, the current dose had been adequately tolerated. Subjects who did not tolerate the study drug during the first 2 weeks of treatment (ie, 2 mg perampanel or placebo once daily) were to be withdrawn and not replaced. Subjects who did not tolerate the study drug from the third to the twelfth week of treatment (ie, 4, 6, 8, 10, or 12 mg perampanel) could have remained on the same dose or had their dose reduced to their previously tolerated dose (subjects receiving placebo were to have a sham down-titration). Only 1 dose reduction was to be allowed, and any subject requiring more than 1 dose reduction was to be withdrawn and was not to be replaced. Any subject judged to require dose reduction between visits was to return to the study center for an unscheduled visit. During this phase, a blood sample for plasma concentrations of concomitant AEDs was to be obtained at Visit 2 (Day 1).
- Maintenance Phase (4 weeks, Days 85 to 112): During the Maintenance Phase, the subject was to continue using the final dose reached during the Titration Phase. No further dose reductions were to be allowed, although the investigator retained the option to withdraw the subject at any time. At the end of the Maintenance Phase (Day 113), blood samples for plasma concentrations of perampanel and other concomitant AEDs were to be obtained for PK analysis. During this phase, blood samples for plasma concentrations of perampanel and concomitant AEDs were to be obtained at Visits 8, 9, or at a Premature Discontinuation Visit (if applicable).
- Follow-up Phase (4 weeks, Day 113 to 141): All subjects were to return for end-of-study assessments.

Subjects were to return to the study center for monitoring during dose-titration steps (Days 15, 29, 43, 57, 71), at the end of the Titration Phase (Day 85), and at the end of the Maintenance Phase (Day 113). During the dose-titration steps, subjects were to be observed in the study center and discharged at the discretion of the investigator. An observation period of 2 hours after dosing was required. All subjects were to be contacted by telephone on the day following dose administration and again at the midpoint of the 4-week Maintenance Phase (ie, Days 2, 16, 30, 44, 58, 72, 86, and 100) to determine if any adverse events had occurred following dosing at the new dose level.

Number of Subjects (Planned and Analyzed):

- 48 subjects were planned
- 55 subjects were screened and 48 subjects were enrolled and randomized
- 38 subjects were randomized to the perampanel group and 10 subjects were randomized to the placebo group
- 48 subjects were analyzed for safety (ie, all randomized subjects)
- 47 subjects were analyzed for efficacy (1 subject, subject PPD in the placebo group, was excluded from the ITT population due to an invalid baseline seizure diary)

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were male or female aged 18 to 70 years, inclusive, with the diagnosis of epilepsy with

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

Test Product, Dose and Mode of Administration, Lot Number:
perampanel, 2 mg tablets, oral, Lot # P57004ZZA

Duration of Treatment: 16 weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:
Matching placebo, tablets, oral, Lot # P57002ZZA

Criteria for Evaluation:

Efficacy:
Seizure counts (recorded in a diary); Clinical Global Impression of Change; and Patient Global Impression of Change.

Dose Tolerability and PK:

Tolerability of dose (maximum tolerated dose [MTD]) and concomitant anti-epileptic drug (AED) plasma concentrations.

Safety:
Physical and neurological examination; adverse events (AEs); orthostatic vital signs; ECG; and laboratory assessments.

Statistical Methods:
Analysis populations were the Safety Population, the Intent-to-Treat (ITT) Population, and the Fully Evaluable (FE) Population. The primary efficacy analysis was performed on the ITT Population.

Efficacy:
The primary efficacy endpoint was the proportion of responders in the active treatment group during the Maintenance Phase (last observation carried forward [LOCF]; see Section 9.8.2.3). A subject was said to have been a responder for a time period if she/he experienced a 50% or greater reduction in seizure frequency per 28 days from the Baseline Phase. Seizure frequency was based on the total number of seizures during that period (as recorded in the subject's diary), rescaled to a 28-day-frequency.

Secondary efficacy endpoints were:

1. Proportion of responders during the Maintenance Phase, Maintenance observed cases (OC), the Titration Phase, each dose phase (2-mg dose phase, 4-mg dose phase, …, 12-mg dose phase), the Overall Treatment Phase (= 12-week Titration Phase plus 4-week Maintenance Phase), 6-week Maintenance (= last 2 weeks of the Titration Phase plus the Maintenance Phase), and the Follow-up Phase.
2. Percentage change in seizure frequency per 28 days from the Baseline Phase to each of the same phases

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listed in item (1) above.

3. Proportion of subjects experiencing 0 to 25%, > 25% to 50%, > 50% to 75%, > 75% to 100% reduction/increase and > 100% increase in seizure frequency per 28 days from the Baseline Phase to each of the same phases listed in item (1) above.
4. Number of days without seizures per 28 days (during each of the same phases listed in item (1) above.
5. Change from baseline in the Clinician's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.
6. Change from baseline in the Patient's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.

Exploratory efficacy endpoints were:

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

An ad hoc efficacy endpoint was a time-to-event analysis of times to the 1st, 3rd, 6th, 9th, and 12th seizure.

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

Summary of Results

Efficacy:

- For perampanel doses up to 12 mg
  - Median % seizure reduction from baseline:

    40% median seizure reduction in the perampanel group (N=38) and 2% median seizure increase in the placebo group (N=9); 42% difference of seizure reduction in the perampanel group over the placebo group in the Overall Treatment Phase
  - Responder rate:

    40% in the perampanel group (N=38) and 22% in the placebo group (N=9); 18% difference in the proportion of responders in the perampanel group compared to the placebo group in the Overall Treatment Phase

Based on the small sample size estimates, approximately 60% of the subjects are estimated to tolerate the 8 mg dose group relative to placebo (47%-55% in the perampanel group, 70%-88% in the placebo group); 45% subjects are estimated to tolerate the 12 mg dose relative to placebo (29%-44% in the perampanel group, 60%-88% in the placebo group). Due to the small sample size, analysis of the placebo dose group may not be reliable, hence, caution is recommended when interpreting these results.

This study was not powered to detect statistical significance in any of the efficacy endpoints. In general, the results of the efficacy analyses based on the Overall Treatment Phase are more favorable towards perampanel compared to placebo (39.5% vs 22.2% for responder rate; 39.6% vs −2.1% for median % reduction from baseline).

Numerically, the 8-mg phase is shown to have the highest reduction in median % change and highest

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responder rate. The 10-mg and 12-mg dose groups appear to be better; however, sample sizes are too small to make reliable conclusions.

Perampanel had a numerically higher percentage of subjects with improvement (minimally, much, and very much improved) compared to placebo in both the Clinical Global Impression of Change (57.9% vs 44.4%) and the Patient Global Impression of Change (62.1% vs 44.4%) at the end of the treatment.

Safety:

- No drug-related serious adverse events (SAEs) occurred at any dose studied. The percentages of subjects having severe adverse events (AEs) were 13.2% (5/38) in the perampanel group and 0% (0/10) in the placebo group. The severe AEs in 3 out of 5 subjects (7.8%, 3/38) were deemed not possibly/probably related by the investigators and in 2 out of 5 subjects were deemed not related. In contrast, the percentages of subjects having treatment-emergent SAEs were 2.6% (1/38) in the perampanel group and 10.0% (1/10) in the placebo group. There were a total of 2 treatment-emergent SAEs: 1 seizure cluster in a subject in the placebo group and 1 colonic polyp in a subject in the perampanel group. Both SAEs were deemed not related to the study drug.
- No differences in early discontinuations due to AEs were observed between the treatment groups. The percentage of subjects having treatment-emergent AEs (TEAEs) leading to discontinuation from the study was comparable between the treatment groups (5.3% in the perampanel group and 10.0% in the placebo group).
- The overall incidence of TEAEs was similar between treatment groups (84.2% perampanel and 80.0% placebo). A slightly higher percentage of subjects in the perampanel group vs the placebo group had TEAEs that were possibly related to treatment (55.3% vs 40.0%, respectively), but these were mostly mild to moderate in nature and were resolved. While a higher percentage of subjects in the perampanel group vs the placebo group had TEAEs that were probably related to treatment (47.4% vs 0.0%, respectively).
- No differences in the perampanel and placebo treatment groups with regard to hepatic and renal function, blood chemistry and hematology values, vital signs, physical and neurological examinations, weight, ECG were observed.
- Although dizziness and somnolence occurred more frequently in subjects in the perampanel group, this was consistent with the known safety profile of perampanel.
- No new signals regarding the safety profile of perampanel emerged from this study.

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CONCLUSIONS:

Efficacy

- Efficacy data showed a trend that is within the range of other anti-epileptic medications
- The observed efficacy trend was consistent with the results seen in another Phase 2 epilepsy study (E2007-A001-206)

Dose Tolerability

Eight (8) mg appears to be well tolerated and efficacious; a subgroup of subjects can also tolerate higher doses up to 12 mg. Based on this small sample size and short duration study, there is a potential of higher efficacy, in general, among the subjects who reach higher doses. Given the potential benefit to some subjects and relatively low safety risk, it is desirable to explore 8 mg and 12 mg doses further in Phase 3 studies.

Safety

- Subjects who reached 12 mg tolerated the dose well
- No drug-related SAEs at any doses studied
- No between-group difference in early discontinuation from the study due to AEs

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