2 SYNOPSIS

Sponsor: **Eisai Medical Research Inc** **Name of Finished Product:** **product name E2007** **Name of Active Ingredient:** **perampanel**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Study Title:
A Double-Blind, Placebo-Controlled, Dose -Escalation, Parallel-Group Study of E2007 Given as Adjunctive Therapy in Patients with Refractory Partial Seizures

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): Not applicable (see Appendix 16.1.11)

Studied Period:

08 March 2005 (first subject enrolled) to
06 February 2007 (last subject completed)

Study Phase: 2

Objectives: The primary objective of this study was to determine the maximal tolerated dose (MTD) of E2007 given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures).

The secondary objectives were to evaluate the safety, efficacy, concentration-efficacy relationship, and pharmacokinetics of E2007 and the effects of E2007 on the Profile of Mood States (POMS) test.

Methodology: The trial was a double-blind, placebo-controlled, dose-escalation, parallel-group study with 3 arms: Drug-treated using BID dosing, drug-treated using QD dosing and placebo-treated. Within groups, subjects were stratified 1:1 according to their concomitant antiepileptic medication(s) (AEDs) into one of 2 categories: (1) induced (treated with one or a maximum of 2 marketed and approved antiepileptic inducer medications such as carbamazepine, phenytoin, phenobarbital, or primidone) and (2) non-induced (treated with one or a maximum of 2 marketed and approved antiepileptic non-inducer medications such as topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or levetiracetam, and none of the drugs in the induced group). To be enrolled, a 4 week retrospective Baseline using the subject's seizure calendar was evaluated. The study consisted of the following phases:

1. **Baseline Phase** (4 weeks): Prospective ascertainment of seizure frequency based on the subject's seizure calendar.
2. **Titration Phase** (up to 8 weeks): Subjects were titrated from a starting dose of 1 mg/day (0.5 mg BID or 1 mg QD). The dose was increased every 2 weeks up to 4 mg/day or the MTD. Subjects suffering intolerable adverse events (AEs) were to have the dose reduced one step. Once reduced, the same dose was to be continued until the end of the Maintenance Phase (see below). Pharmacokinetic (PK) samples were obtained at each visit.
3. **Maintenance Phase** (4 weeks): The E2007 dose was given at the MTD that each subject maintained during the Titration Phase, and PK samples were obtained at each visit. At the last Maintenance Visit, all completing subjects (including the placebo group) were started on 1 mg/day of the study drug.
4. **Transition Phase** (2 weeks): Subjects were maintained on 1 mg/day of study drug. After 2 weeks, a final visit was conducted and subjects were withdrawn from study drug treatment. Subjects were to return for the Safety Visit 4 weeks later.

Number of Patients (Planned and Analyzed): 144 subjects were planned; 153 subjects were analyzed for safety; 152 subjects were analyzed for efficacy.

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Diagnosis and Main Criteria for Inclusion: Male and nonpregnant females who had a diagnosis of refractory partial seizures, were treated with 1 or a maximum of 2 other AEDs, and met all other inclusion criteria and none of the exclusion criteria.

Test Product, Dose and Mode of Administration, Lot Number: The study drug, E2007, was formulated as 0.5 mg, 1 mg and 2 mg tablets and packaged in child-resistant blister packs. Tablets were 0.5 mg (lot numbers P33007ZZF and P48003ZZA), 1 mg (lot number P48004ZZA), or 2 mg (lot number P48005ZZA) each and were taken orally QD or BID.

Duration of Treatment:

14 weeks (8-week Titration, 4-week Maintenance and 2-week Transition Phases)

Reference Therapy, Dose and Mode of Administration, Lot Number:

Reference therapy: Matching placebo tablets in child-resistant blister packs, taken orally. The lot number was P48001ZZA.

Criteria for Evaluation:

Efficacy was assessed by seizure counts (subject's diary), Clinical Global Impression of Change (CGI), Patient's Global Impression of Change (PGI) and the Seizure Severity Questionnaire.

Primary Endpoint:

Determination of the maximum tolerated dose (MTD) for each subject was a primary study endpoint. For the trial the MTD was defined as the maximum tolerated dose by the majority of the subjects up to a maximum of 4 mg per day.

Efficacy:

The proportion of responders during the Maintenance Phase (LOCF) in the Intent-to-Treat (ITT) Population constituted the primary endpoint analysis.

Pharmacokinetics:

E2007 plasma concentration-time data were reported in tabular and graphical form.

Safety:

Safety was evaluated using frequency and severity of adverse events (AEs); physical, neurological and ophthalmological (at selected sites) examinations; 12-lead electrocardiogram (ECG); and laboratory assessments including hematology, clinical chemistry and urinalysis during the trial period.

Statistical Methods:

Data analysis, tabulations of descriptive statistics and inferential statistics were performed using SAS.

The following subject populations were defined for data analyses:

Safety Population: Subjects included in the safety analysis were those who were randomized and took at least one dose of double-blind study drug.

Intent-To-Treat Population: Subjects included in the ITT analysis were those who both were included in the Safety Population and had at least 2 weeks of Baseline, and had at least one week of Titration and/or Maintenance seizure frequency data.

Per Protocol/Fully Evaluable Population: Subjects included in the Per Protocol/Fully Evaluable (FE) analysis were those who were included in the ITT Population, did not have any major protocol deviations/violations and were at least 80% compliant with the study drug at Week 13 as well as during the entire Maintenance Phase.

Efficacy:

The primary efficacy variable was the proportion of responders in the ITT-LOCF Population in the Maintenance

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Phase. A subject was a responder if they experienced a 50% or greater reduction in seizure frequency from the Baseline Phase. Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.

Statistical significance at $\alpha < 0.05$ (2-sided) in the ITT-LOCF Population was required to establish the efficacy of E2007 vs. placebo. Supportive analyses of the ITT-LOCF and FE Populations were conducted for secondary efficacy measures. Other secondary efficacy endpoints included assessments of the proportion of responders at other intervals and for subsets of the ITT Population, the percent change in seizure frequency from baseline, seizure freedom, seizure severity, and subjective assessments of the subjects' improvement during the study (CGIC and PGIC) and of their mood (POMS).

Categorical variables (proportion of responders, percent reduction in seizure frequency, percent of subjects who achieve seizure-free status, no significant change in seizure frequency, significant increase in seizures, CGIC, PGIC, and the percentage of subjects needing back titration) were analyzed by using a CMH test stratified by center. Continuous variables (percent change in seizure frequency and the percent change in partial seizure frequency, the number of seizure-free days per 28 days, changes in the Seizure Severity Questionnaire) were analyzed by using ranked ANOVA with terms for treatment and center in the model.

Safety:
Descriptive statistics were summarized for all parameters. Changes from baseline were analyzed for clinical laboratory data, vital signs, and ECG findings.

Summary of Results

Primary Endpoint:
In the ITT population, the MTD for the majority of subjects in both the perampanel and placebo groups (83.2% and 82.4%, respectively) was 4mg/day, the highest dose available in this study. This was also the MTD for the majority of the subjects who received E2007 in the induced and non-induced, and in the QD and BID dosing, subgroups.

Efficacy:
The primary efficacy variable was the proportion of responders in the Maintenance Phase (LOCF). A subject is a responder if they experience a 50% or greater reduction in seizure frequency from the Baseline Phase. The responder rate was 30.7% for the E2007 treatment group and 21.6% for the placebo group (p=0.1894). A secondary efficacy variable was the median percentage seizure reduction and showed approximately 26% improvement in E2007 and 19% improvement in the placebo in the Maintenance Phase (LOCF). In summary, E2007 at 4 mg/day shows a trend in antiepileptic effect in the studied population. The efficacy at 4 mg is in the range of other antiepileptic drugs when studied in their lower dose range.

Pharmacokinetics:
Inducers of P450 have a marked effect on E2007 blood levels as anticipated. In contrast E2007 does not alter the levels of the AEDs used in this study.

Safety:
The percentage of subjects with 1 or more treatment-emergent AEs was similar in the E2007 treatment group (66.7%, 68 of 102 subjects) and placebo treatment group (62.7%, 32 of 51 subjects). The percentage of subjects with possibly or probably related treatment-emergent AEs was slightly higher in the placebo treatment group (49.0%) than in the E2007 treatment group (38.2%). In both treatment groups, the majority of AEs were mild or moderate in severity. The occurrence rates of dizziness and somnolence (anticipated AEs of E2007) in the E2007 group were similar to those in the placebo group (dizziness: 13.7% in E2007 and 15.7% in placebo; somnolence:

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7.8% in E2007 and 9.8% in placebo subjects). The other most frequent treatment-emergent AEs reported for subjects were headache (9.8% of E2007 subjects vs 13.7% of placebo subjects), contusion ([investigator terms included bruise, bruised or bruising secondary due to seizure] 6.9% of E2007 subjects vs 3.9% of placebo subjects), and fatigue (5.9% of E2007 subjects vs 5.9% of placebo subjects).

There were no deaths during the study. The occurrence rate of treatment-emergent SAEs was 2.0% (2/102 subjects) in the E2007 treatment group and 3.9% (2/51 subjects) in the placebo group. There were a total of 5 serious adverse events (SAEs) experienced by 4 subjects, all connected to seizures: both mental status changes and postictal state for 1 subject (confounded by toxicity from Dilantin) and status epilepticus for 1 subject in the E2007 treatment group and convulsion for 1 subject and status epilepticus for 1 subject in the placebo group. The majority of events were considered severe in severity and all 5 events were considered possibly treatment-related. An additional subject in the placebo group experienced an SAE (convulsion) during baseline. The subjects prematurely terminated from the study due to treatment-emergent adverse events were similar in the E2007 (5.9%; 6/102 subjects) and placebo (3.9%; 2/51 subjects) groups. An additional subject in the placebo group withdrew from the study due to an AE that was present at Baseline.

There were no marked differences in the occurrence of treatment-emergent AEs, or in possibly or probably related treatment-emergent AEs, between the E2007-treated subjects in the non-induced (63.2% all, 40.4% related) and induced subgroups (71.1% all, 35.6% related).

There were no clinically relevant differences in the blood chemistry and hematology values between placebo and E2007. There were no clinically relevant changes in ECG between the E2007 and placebo groups.

Based on the overall AE profile, E2007 at a 4 mg dose was well-tolerated.

CONCLUSIONS

Efficacy:

- E2007 at 4 mg shows a trend (30.7% in E2007 vs. 21.6% in placebo, p=0.1894 for the primary analysis of 50% responder rate) in antiepileptic effect in the studied population during the Maintenance Phase (LOCF).
- The secondary efficacy endpoint (median percentage seizure reduction) showed approximately 26% improvement in E2007 and 19% improvement in the placebo during the Maintenance Phase (LOCF).
- An observed efficacy at 4 mg is in the range of other antiepileptic drugs when studied in their lower dose range.

Safety:

- E2007 at a 4 mg dose was well-tolerated.
- Based on the overall AE profile and other safety and tolerability results obtained within the E2007 program, the maximum tolerated dose of E2007 has not been reached in this trial.

Overall:

The data support further development of E2007 in this indication. Higher dose levels of E2007 need to be tested to identify the maximum effective doses as shown in other antiepileptic drugs.

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