# 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor Company:** Eisai Limited<br>**Name of Finished Product:** Zonegran™<br>**Name of Active Ingredient:** Zonisamide | Individual Study Table Referring to Part of the Dossier<br>Volume:<br>Page: | (For National Authority Use Only) |
| **Title of Study:** An open-label study of Zonegran™ (zonisamide) in patients with partial onset seizures. | | |
| **Study Number:** E2090-E044-401 | | |
| **Investigator:** 101 sites.<br>Principal Investigator: Dr. Sophie Dupont, Hôpital Pitié Salpêtrière, 47 bd de l'hôpital, Paris 75651, France. | | |
| **Study center:** Austria 4 sites, Denmark 3 sites, Finland 2 sites, France 34 sites, Germany 18 sites, Italy 28 sites, The Netherlands 1 site, Norway 3 sites, Sweden 3 sites, UK 5 sites. | | |
| **Study Period:** 01 March 2006 to 23 August 2007 (18 months) | | **Clinical Phase:** IV |
| **Objective:** To determine the efficacy and safety of adjunctive open label Zonegran™ treatment in patients with refractory partial seizures. | | |
| **Methodology:** Prior to any study procedures or evaluations, written informed consent was obtained. At the screening visit, medical and neurological history, physical and neurological examinations, laboratory safety profile, vital signs and the number of monthly seizures were assessed. Eligible patients were dispensed study drug (initial dose 50mg/day, bid) at the baseline visit. Patients visited the clinics at regular intervals (Weeks 1, 8, 14 and 19) and also received monitoring telephone calls from site staff. During the treatment phase (19 weeks) the dose was titrated to at least 300mg/day bid but could be reduced to 200mg/day bid in case of tolerability issues. The maximum dose allowed in the study was 500mg/day bid. There were two fixed dose periods, during which no titration was allowed: the first fixed dose period was from Weeks 10 to 13, and the second fixed dose period was from Weeks 16 to 19. The final assessment visit was conducted at the end of Week 19. At this point, patients either continued on prescription Zonegran™ as arranged by the Investigator, or down titrated Zonegran™ at the recommended rate of 100mg/week. If applicable, a follow up visit was conducted on the last day of dosing in the down titration period. | | |
| **Number of Subjects:** Planned: 1000 patients<br>Actual: 317 patients enrolled (281 included in the safety/intent-to-treat [ITT] population and 213 included in the Per Protocol [PP] population) | | |
| **Diagnosis and Criteria for Inclusion:** Male or female epilepsy patients aged 18-75 years old with partial onset seizures (simple and/or complex) with or without secondary generalization according to the International League against Epilepsy (ILAE) criteria. Patients had to have at least 4 seizures during the 8-week screening period and had to be receiving at least 1 but no more than 2 other anti-epileptic drugs as concomitant medication, with the dose being stable for at least 8 weeks before the baseline visit. | | |
| **Test Product, Dose and Mode of Administration, Lot Number, Expiry Date:** All patients were treated with Zonegran™. The starting dose was 50mg/day bid orally for the first week. Patients were then titrated up to a maximum 500mg/day bid by the end of Week 19. 25mg, 50mg and 100mg capsules were provided Batch numbers: 25mg - 42463 and 5001A; 50mg - 42475; 100mg - 5201B and 42410. | | |
| **Reference Product, Dose and Mode of Administration, Lot Number, Expiry Date:** Not applicable. | | |
| **Duration of Treatment:** Maximum duration in the study was 32 weeks (8 weeks screening, 19 weeks treatment with Zonegran™ and up to 5 weeks down titration phase for patients not continuing on prescribed Zonegran™). | | |
| **Criteria for Evaluation:** The primary endpoint was the change from baseline to the end of Week 19 in partial seizure frequency. The secondary endpoints included the proportion of responders (defined as patients with at least 50% reduction from baseline in seizure frequency), clinician's global impression of change (CGI scale), and assessment of Quality of Life using the QOLIE-31 and the Liverpool Seizure Severity scale (LSSS).<br>Tolerability and safety were assessed by monitoring observed and reported adverse events (AEs), vital signs, change in physical/neurological examination and clinical laboratory data. | | |

| | | |
|---|---|---|
| **Name of Sponsor Company:** Eisai Limited | Individual Study Table Referring to Part of the Dossier | (For National Authority Use Only) |
| **Name of Finished Product:** Zonegran™ | Volume: | |
| **Name of Active Ingredient:** Zonisamide | Page: | |

**Statistical Methods:** As this study was open and uncontrolled, the statistical analyses only provide guidance to possible treatment related effects.
Efficacy Analysis: Efficacy analyses were performed on the ITT and PP populations. Analyses were done on the observed cases (OC) and on the last observations carried forward (LOCF) data. Efficacy endpoints were analyzed using ANCOVA method, with covariates of baseline seizure frequency, country and sex being included. The least square means and 95% confidence interval (CI) from this analysis were to be presented but the data were not found to be normally distributed, so median values with 95% non-parametric confidence intervals are presented instead. No p-values are presented as the analyses were non-comparative.
Safety Analysis: Frequency and percentage of treatment-emergent AEs (TEAEs) and summary statistics of vital signs and laboratory assessments are presented by timepoint.

**RESULTS:**
The study was originally designed to recruit 1000 patients. However, due to a lack of availability of Zonegran™ stock for the study, some sites could not be initiated and recruitment was constrained in other countries. Zonegran™ was then launched onto the market in various countries so recruitment was halted at 317 patients and the focus of the statistical analysis was changed to analyze the overall Zonegran™ cohort rather than to compare efficacy results from individual doses. It was considered that the total recruitment of 317 patients would provide sufficient power to achieve this.

**Efficacy:**

- The median number of monthly seizures was reduced from 6 to approximately 4 by Weeks 10-13, a level which was sustained during the 2nd fixed period (Weeks 16-19).
- More than 40% of patients had at least a 50% reduction in their monthly seizure frequency during the first and second fixed dose periods. Approximately 15% of the patients had a 100% reduction in their monthly seizure frequency during the second fixed dose period.
- At the final visit, 74% of the patients evaluated rated an improvement using the Clinician's Global Impression Scale (CGI) (95% CI: 66.9 to 80.7).
- Some improvement in QOL was detected using the LSSS assessment scale. No marked changes were seen in QOL parameters using the QOLIE-31.
- In order to assess the impact of withdrawal and missing assessments, the LOCF method was applied and analyzed. The results for this analysis were similar to that of the main analysis.
- The results in the PP population reflected those seen in the ITT population.

**Safety:**

- In general, Zonegran™ was well tolerated. The most common TEAE was fatigue (experienced by 16.7% of patients), followed by somnolence (experienced by 15.3% of patients). Other TEAEs experienced by ≥5% of patients were headache, asthenia, nausea, insomnia, dizziness and vertigo.
- 26 patients (12.4%) reported at least one severe TEAE. The severe TEAEs reported in more than one patient were somnolence (4 patients), convulsions (3 patients), and headache, disturbance in attention, asthenia and insomnia (each in 2 patients).
- Most of the patients had AEs that were considered drug-related, which is not uncommon in an open-label study.
- No deaths occurred during the study.
- Sixteen patients (5.7%) had TESAEs during the study. The most common TESAE was convulsions (3 patients), grand mal convulsions (2 patients) and psychotic disorder (2 patients). Only 7 TESAEs were considered drug-related.
- 43 patients (15.3%) had TEAEs that led to withdrawal from the study. The most common TEAE leading to withdrawal from the study was somnolence, with this event leading to withdrawal of 9 patients (3.2%).

| | | |
|---|---|---|
| **Name of Sponsor Company:** Eisai Limited | Individual Study Table Referring to Part of the Dossier | (For National Authority Use Only) |
| **Name of Finished Product:** Zonegran™ | Volume: | |
| **Name of Active Ingredient:** Zonisamide | Page: | |

- Small changes were noted in some laboratory parameters but none were considered clinically relevant.
- Some changes were noted during the study in vital signs and physical and neurological examination findings but none were considered clinically relevant.

**CONCLUSIONS:**

- In this study a reduction in seizure frequency, with at least 40% of patients having a 50% or greater reduction in seizure frequency compared to baseline, was observed, as well as an improvement in seizure severity. The reduction in seizure frequency and percentage responders observed in this study are consistent with previous findings from placebo-controlled studies with Zonegran™.
- Zonegran™ was generally well tolerated at doses ranging from 200mg to 500mg per day. The most common TEAEs were fatigue and somnolence, with these events leading to withdrawal from the study of some patients.
- No deaths occurred during the study and only 7 patients had TESAEs that were considered related to the study drug.

**Date of the Report:** 28 July 2009