2. STUDY SYNOPSIS

Title of Study: A Multicentre, Randomised, Active Comparator, Parallel Group Study to Compare the Effect on Cognition of Adjunctive Therapy with Zonisamide Versus Sodium Valproate

Investigators: Recruited subjects – Dr. P Marusic and Dr. A Czlonkowska. Did not recruit subjects – Dr. J Majkowski, Dr. Z Stelmasiak, Dr. W Fryze, Dr. J Kochanowicz, Dr. C Elger, Dr. H Stefan, Dr. N Lang, Dr. P Halasz, Dr. J Nikl, Dr. A Valikovics, Dr. A Escartin, Dr. V Iváñez, Dr. R Kälviäinen, Dr. E Trinka, Dr. HJM Majoie, Dr. B Engelsen, Dr. J Lopes.

Principal Investigator: Professor AP Aldenkamp

Study Centres: Two study centres recruited subjects (1 in the Czech Republic and 1 in Poland). A further 17 study centres in Europe were initiated – Poland (4 centres), Germany (3 centres), Hungary (3 centres), Spain (2 centres), Finland (1 centre), Austria (1 centre), Netherlands (1 centre), Norway (1 centre), and Portugal (1 centre).

Publications: None

Studied Period: 23 July 2008 to 17 December 2008 | **Clinical Phase**: Phase IV

Objective: To assess the effects of zonisamide on cognition, when administered as adjunctive treatment to adults with refractory partial epilepsy taking fixed dose carbamazepine monotherapy, in comparison with adjunctive sodium valproate.

Methodology: This was a 2 arm, randomised, active comparator, parallel group study. The study consisted of a baseline period (3 days for subjects whose seizure history was well documented prior to the Randomization Visit or 4 weeks for other subjects), a titration and flexible dosing period (10 weeks; Weeks 1 to 10), and a fixed dose period (2 weeks; Weeks 11 and 12). At the end of the baseline period, subjects were randomised to zonisamide or sodium valproate. Subjects had to be taking a fixed dose of carbamazepine for at least 6 weeks prior to randomisation, and the dose of carbamazepine had to remain unchanged until the final assessments at Week 12. During the titration and flexible dosing period, randomised treatment was titrated to the minimally effective dose, the maximum tolerated dose, or the maximum allowed dose (500mg/day for zonisamide and 2500mg/day for sodium valproate), whichever was the lowest. Subjects remained on this fixed dose of zonisamide/sodium valproate during the fixed dose period (Weeks 11 and 12). The primary cognitive evaluation was completed at the end of the fixed dose period (Week 12). Following the fixed dose period, subjects could down titrate or switch to marketed zonisamide/sodium valproate.

Number of Subjects: Approximately 80 subjects were planned. However, this study was terminated early in November 2008 at the Sponsor's discretion. When the decision was made to terminate the study, only 2 subjects had been enrolled. Therefore, no analysis has been performed. Data are listed only.

Diagnosis and Criteria for Inclusion: To qualify for study participation, subjects had to have a clinical diagnosis of idiopathic/cryptogenic/non progressive symptomatic localisation-related epilepsy with partial onset seizures with or without secondary generalisation, be able to understand and be willing to sign an informed consent form, be ≥18 years of age, be taking carbamazepine as monotherapy at baseline, and require addition of another anti-epileptic drug (AED). In addition, female subjects of childbearing potential could not be pregnant or lactating, and had to use a medically acceptable form of contraception during the study and for at least 1 month after discontinuation of study drug. Subjects could also not have received previous treatment with sodium valproate (> 4 weeks usage) or previous treatment with zonisamide, used an AED other than carbamazepine less than 6 weeks prior to randomisation, or use an AED other than carbamazepine, zonisamide or sodium valproate during the study.

Test Product, Dose, Mode of Administration, Batch Nos:
Zonisamide, 50 to 500mg/day, Oral
Provided as capsules:

	Batch Numbers
25mg	53546
50mg	53533
100mg	53820

Duration of Treatment: 12 to 16 weeks. For zonisamide, dosing started at 50mg/day and was increased, during the titration and flexible dosing period (10 weeks), to the minimally effective dose, maximum tolerated dose or 500mg/day, whichever was the lowest. The minimum permitted maintenance dose was 200mg/day. For sodium valproate, dosing started at 600mg/day and was increased, during the titration and flexible dosing period (10 weeks), to the minimally effective dose, maximum tolerated dose or 2500mg/day, whichever was the lowest. The minimum permitted maintenance dose was 1000mg/day. Subjects remained on the dose determined at Week 10 for the fixed dose period (Weeks 11 and 12). At the end of Week 12, subjects could down titrate (over a period of up to 4 weeks) or switch to marketed zonisamide/sodium valproate.

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Sodium valproate, 600 to 2500mg/day, Oral
Provided as tablets (enteric coated or crushable):

	Batch Numbers
100mg (crushable)	7277269
200mg (enteric coated)	7262131
500mg (enteric coated)	7262129

Criteria for Evaluation: A seizure diary was maintained by each subject from the Screening Visit until the end of Week 12. Safety assessments included neurological examinations, laboratory safety tests (urea and electrolytes, liver function, haematology, and AED level monitoring), vital signs and weight measurements, and collection of any adverse event (AE) and concomitant medication data. In addition, cognitive tests [Ferum Psyche (FePsy) cognitive battery, Profile of Mood States (POMS) or Aldenkamp Baker Neurotoxicity Scale (ABNAS)] were performed at the Randomisation Visit, and at Weeks 6 and 12.

Statistical Methods: As this study was terminated early, no formal statistical analysis has been performed.

SUMMARY – CONCLUSIONS:

RESULTS: Two subjects were enrolled and treated during this study. One subject was randomised to zonisamide and completed the study. He was titrated up to a dose of 200mg/day and remained on this dose for the fixed dose period. The other subject was randomised to sodium valproate. She was titrated up to a dose of 1200mg/day by Day 13 and she was discontinued on that day due to early termination of the study.

Efficacy: The subject treated with zonisamide did not experience any seizures prior to the start of treatment. No data is available regarding seizures during treatment. The subject treated with sodium valproate experienced 2 simple partial seizures during the 34 days prior to the start of treatment and 1 simple partial seizure on Day 12 of treatment.

Safety: No AEs or clinically significant changes in laboratory safety tests, vital signs or weight were reported during this study. One subject (zonisamide) completed cognitive tests at the Randomisation Visit, Week 6 and Week 12. There were no clinically significant changes in the FePsy cognitive battery, POMS or ABNAS assessments during the study.

CONCLUSIONS: This study was terminated early at the Sponsor's discretion. When this study was discontinued, only 2 subjects had been enrolled. One subject completed the study and received 12 weeks of treatment with zonisamide. The other subject received 13 days of treatment with sodium valproate prior to discontinuation due to early termination of the study.

No AEs or clinically significant changes in laboratory safety tests, vital signs or weight were reported during this study. One subject (zonisamide) completed cognitive tests at the Randomisation Visit, Week 6 and Week 12. There were no clinically significant changes in the FePsy, POMS or ABNAS assessments during the study.

No safety issue was observed based on information from these 2 subjects.

Date of Final Report: 09 August 2010