Synopsis – Study 13098A

Study Title A prospective, open-label study of the structure and function of the retina in adult patients with refractory complex partial seizures treated with vigabatrin (Sabril®)
Investigators 18 principal investigators at 18 sites in the United States (US) *Sponsor's responsible medical officer* – [redacted]
Study Sites 18 sites in the US
Publications None (as of the date of this report)
Study Period *First patient first visit* – 22 December 2010 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 1 May 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objectives*: – to evaluate the change in visual fields by means of automated static perimetry in patients with refractory complex partial seizures (rCPS) without prior exposure to vigabatrin – to evaluate the change in retinal structure by means of spectral domain optical coherence tomography (SD-OCT) in patients with rCPS without prior exposure to vigabatrin • *Exploratory objectives*: – to evaluate the visual acuity and color vision in patients newly started on vigabatrin – to evaluate, by means of the 39-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-39), patients' perception of their ability to perform every day activities, in patients newly started on vigabatrin – to evaluate the change in visual fields by means of the tangent corner test (TCT)
Study Methodology • This was an interventional, prospective, multi-site, open-label study in patients with rCPS. • The patients received commercially available vigabatrin as adjunctive therapy for a period of 12 months. • The initial (baseline) safety and ophthalmic assessments were performed at Visit 1, prior to the first dose of vigabatrin. • During the 12-month treatment period, safety assessments including ophthalmic assessments were performed at two visits (Visits 2 and 3) during the first month of treatment, at the end of Month 3 (Visit 4), and thereafter every third month until the Completion Visit at the end of Month 12 (Visits 5, 6, and 7). • A safety follow-up phone call (Visit 8) was to be conducted 30 days after the Completion/Withdrawal Visit. If vigabatrin was discontinued as a result of a benefit-risk discussion, a final ophthalmic follow-up examination (Visit 9) was to take place 3 months after the Completion/Withdrawal Visit. • At Visit 1, a blood sample for the analysis of specific DNA characteristics was collected. In addition, an optional blood sample for exploratory analysis of DNA characteristics was collected from patients that had given separate consent. • At predetermined timepoints, blood samples were collected for analysis of vigabatrin in plasma and for exploratory taurine biomarker analysis.
Number of Patients Planned 80 patients were planned for enrolment.

Diagnosis and Main Selection Criterion

Patients with rCPS who:

- were to begin vigabatrin therapy for the treatment of complex partial seizures
- were ≥18 years of age
- had had complex partial epilepsy with a duration of more than 1 year and no other seizure type within the past year except for partial seizures secondarily generalised
- had failed, because of lack of efficacy, 3 or more treatments including 3 or more anti-epileptic drugs (AEDs) of differing pharmacologic mechanisms administered as monotherapy or polytherapy
- were taking at least 1 AED. A vagal nerve stimulator is not counted as an AED.
- reported an average of 2 or more seizures per month averaged over the prior 3 months
- were deemed by the treating neurologist and ophthalmologist to be able to reliably complete perimetry testing and other study procedures

Investigational Medicinal Product, Dose and Mode of Administration

Vigabatrin – commercially available vigabatrin (Sabril®) tablets. The dose of vigabatrin was determined by the investigator using the guidance provided in the product label.

Duration of Treatment

12 months

Pharmacokinetic/Exploratory Biomarker/Genomic Assessments

- blood sampling for plasma quantification of vigabatrin
- blood sampling for exploratory taurine biomarker analysis
- blood sampling for specific analysis of DNA characteristics
- blood sampling for exploratory analysis of DNA characteristics (separate informed consent)

The results of these assessments are not included in this *Clinical Study Report*.

Safety Assessments

- Visual fields as measured by:
  - Humphrey static perimetry – 30-2 SITA Fast or 30-2 SITA Standard (central visual field; 30 degrees radius)
  - Humphrey static perimetry – full field horizontal meridian (mid visual field; 40 to 70 degrees radius)
  - TCT (far peripheral field; 70 to 120 degrees radius)
- retinal structure (average retinal nerve fiber layer [RNFL] thickness, macular volume, and macular thickness) as measured by SD-OCT
- visual acuity as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) tests
- color vision as assessed by Roth 28
- National Eye Institute Visual Functioning Questionnaire-39 (NEI VFQ-39)
- complete ophthalmic examinations (eye color, standard and slit lamp examination, funduscopic examination, keratometry, tonometry, and assessments of depth perception and ocular motility)
- adverse events (AEs), vital signs, weight, and physical and neurological examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoints*:
  - change in visual fields:
    - change from reference value in mean deviation, as measured by either the 30-2 SITA Fast or the SITA Standard test
  - change in retinal structure
    - change from reference value in average RNFL thickness, as measured by SD-OCT

Endpoints (continued)

- *Exploratory endpoints*:
  - change from baseline of visual acuity (ETDRS) and color vision (Roth 28)
  - change from reference value of:
    - binocular visual field along the horizontal meridian
    - TCT
    - nine sectors for macular thickness (fovea, temporal inner, superior inner, nasal inner, inferior inner, temporal inner, superior outer, nasal outer, inferior outer)
    - total macular volume
  - proportion of patients who meet the protocol-defined criteria for a provisional, confirmed, or persistent case, based on Humphrey Static Perimetry, TCT, or SD-OCT
  - other potentially clinically relevant changes
  - change from baseline of NEI VFQ-39 (general health score and vision targeted overall composite score)
- *Other safety endpoints*:
  - adverse events
  - absolute values and changes from baseline in vital signs and weight
  - potentially clinically significant (PCS) vital signs and weight changes
  - C-SSRS categorisation based on C-CASA definitions

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of investigational medicinal product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid reference value assessment and at least one valid post-reference value assessment
  - *per-protocol set* (PPS) – all patients in the FAS who had finished all planned visits during the study with post-reference values and who did not have major protocol violations (as specified in section 3 in the *Statistical Analysis Plan*)
- Unless otherwise indicated, the ophthalmology analyses were based on the FAS (primary and exploratory endpoints) and the PPS (primary endpoints and visual acuity, horizontal meridian, TCT, and macular volume). The presentations of other safety data were based on the APTS.
- The reference values for the visual test assessments SD-OCT, Humphrey static perimetry, and TCT were defined as the average of the assessments performed at Visits 1, 2, and 3.
- The safety data were summarised by visit using descriptive techniques; changes from the baseline or reference value were also summarised.
- For the primary endpoints, all data were summarised descriptively. In addition, a 2-sided 95% confidence interval was calculated for the mean change from the reference value at each post-reference visit. Individual patient profiles were also created.
- For the exploratory endpoints, all data were summarised descriptively. In addition, the time to first instance of a provisional case was analysed as survival data grouped according to visit. Binary data were analysed as binomial data with visit number as a factor and using the complementary log-log link. Based on the estimated, interval-specific integrated hazards for the intervals between visits, the cumulative rate of provisional cases was calculated for each visit and plotted against visit number. The respective graph of the cumulative hazards estimates was also created.

Statistical Methodology (continued)

- For exploratory analyses of the influence of time and cumulative exposure of vigabatrin, the endpoints are the assessment of mean deviation by SITA 30-2 Fast/Standard by the University of Iowa Visual Field Reading Center (VFRC) normative database, mean deviation by SITA 30-2 Fast/Standard by the HFA normative database, average RNFL thickness, and total macular volume. These endpoints were analysed individually based on separate random regression models. Total average daily dose and visit were used as the fixed effects as a proxy for cumulative exposure. To assess if there were differences between Visit 1 and Visits 2 or 3 in mean deviation (30-2 SITA Fast/Standard) or in average RNFL thickness, an exploratory analysis using mixed model repeated measurements (MMRM) was performed. The variance structure was assumed to be unstructured. Independent variable was *time* in days since the start of treatment (corresponding to each patient's visit).
- For the exploratory endpoints, a patient was considered a provisional, confirmed, or persistent case for analysis purposes if he/she met the following criteria in at least one eye:
  - change in the binocular visual field along the horizontal meridian, based on the central readers' interpretation of the horizontal meridian and other visual field tests over time and clinical experience. The central readers' interpretation will be potentially clinically significant or not clinically significant; or
  - change in the mean deviation >3.0 dB, as measured by the 30-2 SITA Fast or 30-2 SITA Standard test; or
  - change in the mean linear measurement of the TCT, corresponding to >20 degrees constriction; or
  - decrease in average RNFL thickness (mm) >20%; or
  - decrease >20% in any of the nine sectors measured for macular thickness (mm); or
  - decrease in total macular volume (cubic mm) >10%
- If a provisional case occurred, relevant tests were to be performed at a second examination within 4 ± 2 weeks. A confirmed finding was then classified as a confirmed case. Patients whose tests again met the case criteria at the next visit were defined as a persistent case.

Patient Disposition and Analysis Sets

- 65 patients were enrolled and treated – recruitment to the study was stopped before the planned number of 80 patients had been enrolled, since the goal of having at least 20 patients expected to remain in the study for one year had been reached.
- 38 patients completed the study.
- 27 patients withdrew – 13 patients withdrew due to lack of efficacy, 8 withdrew due to adverse events, 4 withdrew due to administrative or other reasons, and 1 patient each withdrew due to withdrawal of consent and protocol violation.
- 65 patients were analysed – 65 patients in the APTS, 55 in the FAS, and 36 in the PPS.

Demography and Baseline Characteristics of the Study Population

- 65 patients were included in the APTS. The patients were between 19 and 69 years of age and the mean age was approximately 40 years. There were slightly more men (57%) than women (43%) and the majority of the patients (85%) were White.
- The majority of the patients (57%) had moderate rCPS, whereas 23% of the patients had severe rCPS as determined by their physician. A total of 39 patients (60%) had a history of epilepsy surgery. The time since onset of rCPS ranged between 3 and 47 years, with a mean time since onset of 23 years.
- At baseline, the 30-2 SITA mean deviation was normal in approximately three-quarters of the patients based on the VFRC database, and in approximately half of the patients based on the HFA database. The majority of the patients had normal baseline visual acuity (83%) and normal baseline RNFL thickness (66%).

Safety Results

- Based on the FAS, the primary analysis of the changes in 30-2 SITA Fast/Standard mean deviation (central visual field) showed a negative mean change from the reference value at most post-reference visits (range for VFRC: -0.28 to 0.08; range for HFA: -0.47 to 0.00), which indicates a decrease in the central visual field. The mean changes were not statistically significant at any visit based on the VFRC normative database. The mean changes were statistically significant in the left eye at Visits 4 and 5 based on the HFA normative database; these changes did not persist with continued treatment. No statistically significant changes were observed bilaterally. No other noticeable differences between the mean deviation results generated using the VFRC or the HFA database were observed.
- Based on the PPS, the the primary analysis of the mean changes in 30-2 SITA Fast/Standard were not statistically significant at any visit.
- The primary analysis of the changes in RNFL thickness using SD-OCT showed that the population mean change in average RNFL thickness increased at all post-reference visits (range: 0.7 to 7.2 for right and/or left eye) and, based on the FAS, these changes were statistically significant at all visits when compared to the reference values. Based on the PPS, these changes were statistically significant at most visits.
- Overall, the results of the exploratory analyses did not indicate a progressive worsening of vision on a population basis.
- Compared to baseline, between 0 and 4% (2 patients) of the patients in the FAS had a worsening in visual acuity, that is, a difference of ≥3 lines deterioration; none of the patients had a worsening in visual acuity at two consecutive visits. Of the patients in the FAS with an abnormal baseline value (visual acuity result below 20/30 in at least one eye), between 0 and 50% (3 patients) had a difference of ≥3 lines improvement in visual acuity. The color vision data could not be evaluated, since many patients had problems in performing the test.
- Between 0 and 8% (3 patients) of the patients in the FAS had a potentially clinically significant worsening in the binocular visual field along the horizontal meridian (mid visual fields) at each post-reference visit, as determined by the central reader. The maximum mean decrease of the vision field width (far visual fields), measured using the TCT, was 3.4 degrees (Visit 7, left eye). For macular thickness, there was generally a slight increase from the reference value at most visits for the 9 sectors of the macula and for total macular volume at all visits.
- In the assessment of *all cases*, only patients with valid baseline values for all the tests, or for at least one test for which the patient became a case, were evaluated (48 patients). Of those patients, the majority (58%) were not classified as cases during the study. Fifteen patients (31%) were classified as *provisional cases*, 4 patients (8%) were classified as *confirmed cases*, and 1 patient (2%) was classified as a *persistent case* (the categories were mutually exclusive).
- Of the 5 patients who were classified as confirmed or persistent cases, 3 patients were classified based on their 30-2 SITA Fast/Standard central visual field results (all unilateral; one was identified at the 3-month timepoint), 1 was classified based on the change in horizontal meridian (mid visual field), and 1 was classified based on the change in TCT (far visual field); the 2 latter cases were bilateral.
- An additional 2 patients met the protocol-defined criteria for a confirmed case but did not have a valid baseline value for the corresponding tests (1 based on the 30-2 SITA Fast/Standard and 1 based on the TCT).
- Two patients had other potentially clinically relevant changes; one had >20% RNFL thinning in two *segments* (nasal inferior segment and nasal superior segment) and one *quadrant* (nasal quadrant) bilaterally at 3 consecutive visits and one had a confirmed average RNFL *thickening* >20%. In total, 20 patients had RNFL thickening >20% in at least one segment or quadrant.
- There were no clinically relevant changes from baseline in the NEI VFQ-39 general health scores or in the vision-targeted overall composite scores in the overall population or in the subgroup of patients with a confirmed/persistent case of visual field defect. This indicates that the patients, including those that met the case criteria, did not experience any changes in their perception of their general health or in their vision based on this scale.

Safety Results (continued)

- The adverse event incidence is summarised below:

	Vigabatrin	
	n	(%)
Patients treated	65	
Patients who died	0	
Patients with treatment-emergent serious AEs (SAEs)	9	13.8
Patients with treatment-emergent adverse events (TEAEs)	53	81.5
Total number of SAEs	20	
Total number of TEAEs	234	

- Overall, vigabatrin was well tolerated. A total of 82% of the patients treated with vigabatrin had one or more TEAEs; the total number of TEAEs was 234. The incidence of adverse events leading to withdrawal was 18%. The only TEAE leading to withdrawal in ≥2 patients was convulsion (6%; worsening of pre-existing seizures). None of the patients died and the number of patients with one or more SAEs was low (9 patients [14%]). Convulsion (worsening of pre-existing seizures) was the only SAE reported by >1 patient (6 patients [9%]).
- The TEAEs with the highest incidence (≥10%) were convulsion (26%), fall (12%), and dizziness (11%). The incidence of *related* TEAEs was 63%. The *related* TEAEs with the highest incidence (≥5%) were convulsion (19%), dizziness (8%), weight increase (8%), somnolence (6%), fatigue (6%), and vision blurred (6%).
- Eight patients had vision-related adverse events (vision blurred [6 patients], visual acuity reduced [1 patient], and visual field test abnormal [1 patient]). None of these events were reported as SAEs.
- Two patients had suicide-related adverse events reported as SAEs (2 suicide attempts and 1 suicidal ideation; all *not related* to vigabatrin). In addition, 1 patient was withdrawn from the study due to suicidal ideation (*probably related* to vigabatrin).
- Based on the C-SSRS data, the majority of the patients had no suicidal ideation or behaviour (85% of the patients with normal mental state and 100% of the patients with non-normal mental state).
- No clinically relevant patterns were seen with respect to the mean changes in vital signs or weight and the incidences of PCS vital sign values or weight changes were low.

Conclusions

- In the static perimetry assessments evaluating central visual field, the mean changes from the reference values for the 30-2 SITA mean deviation indicated a slight decrease in the central visual field.
- Individual cases of visual field defects (based on 30-2 SITA, horizontal meridian, and TCT) were identified by exploratory analyses; these developed with no observable pattern of onset.
- In the evaluation of retinal structure, the mean changes from the reference values for the average RNFL did not indicate a pattern of thinning. However, thickening of the average RNFL was observed at most visits. The thickening is of uncertain clinical significance. None of the patients had a thinning of the average RNFL of >20% compared to the reference value.
- Up to one year of treatment with vigabatrin did not lead to a confirmed worsening of visual acuity, that is, a worsening of at least 3 lines at two consecutive visits.
- The NEI VFQ-39 scores indicated that the patients did not experience any changes in their perception of their general health or in their vision.
- In the evaluation of far visual fields, small mean changes from the reference value were observed for the TCT, but the clinical relevance of this is uncertain.
- Vigabatrin was well tolerated and there were no new safety findings in the study.

Report Date

22 October 2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.