EMA/CHMP/345694/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zonegran

zonisamide

Procedure No.: EMEA/H/C/000577/II/0059

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai Ltd. submitted to the European Medicines Agency on 29 June 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Zonegran	zonisamide	See Annex A

The following variation was requested:

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed to extend the approved indication of adjunctive treatment of partial seizures with or without secondary generalisation in adults to include monotherapy in adults with newly diagnosed epilepsy in the SmPC and PL. To include subheadings for each of the warnings in section 4.4 of the SmPC in line with version 7.3.1 of the QRD template.To clarify the boxed-warning relating to Stevens-Johnson syndrome in section 4.4 of the SmPC and extend it to include Toxic Epidermal Necrolysis.To update the version number of the RMP in Annex II to version 5.0.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Rapporteur: Patrick Salmon

CoRapporteur: Barbara van Zwieten-Boot

1.2. Steps taken for the assessment

Submission date:	29 June 2011
Start of procedure:	24 July 2011
Rapporteur's preliminary assessment report circulated on:	16 September 2011
CoRapporteur's preliminary assessment report circulated on:	16 September 2011
Joint updated assessment report circulated on:	14 October 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 October 2011
MAH's responses submitted to the CHMP on:	9 December 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 January 2012
Joint Rapporteur's and CoRapporteur's assessment report on the MAH's responses	2 February 2012

circulated on:	
2nd Request for supplementary information adopted by the CHMP on:	16 February 2012
MAH's responses submitted to the CHMP on:	17 April 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 May 2011
An Oral explanation took place on:	22 May 2012
CHMP opinion:	24 May 2012

2. Scientific discussion

2.1. Introduction

Zonegran contains zonisamide, a well-know anti-epileptic agent. It has been authorised in the EU in 2005 for the indication adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

The mechanism of action of zonisamide is not fully elucidated. Zonisamide appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

The staring does is 50 mg in two divided doses. After one week the dose may be increased to 100 mg daily. Thereafter, the dose may be increased at weekly intervals in increments of up to 100 mg. Doses of 300 mg to 500 mg per day have been shown to be effective in the add-on setting. Once the dose is established, zonisamide can be administered once or twice daily.

At present there are 4 antiepileptic agents used in monotherapy. The most commonly used antiepileptics in monotherapy are carbamazepine and valproate. The first choice monotherapy drug for partial epilepsy is carbamazepine, which accounts for over 60% of prescriptions. However in a proportion of patients, usage of these established treatments may be limited by unwanted side effects, pharmacokinetic interactions, multiple doses each day and/or lack of efficacy. The addition of another monotherapy agent could be useful.

Zonisamide is generally well tolerated with the potential for titration without some of the side effects observed with current first line therapy treatments. Furthermore, zonisamide has a pharmacokinetic profile, with a long half-life, permitting once daily dosing.

The current variation concerns the extension of the indication to monotherapy i.e.

"Monotherapy in the treatment of newly diagnosed epilepsy in adults affected by partial seizures with or without secondary generalization."

2.2. Quality aspects

Not applicable.

2.3. Non-clinical aspects

2.3.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment was first conducted for zonisamide in April 2003, in support of the Marketing Authorisation Application for Zonegran Hard Capsules.

A new environmental risk assessment was conducted in December 2008 to include the use of Zonegran Orodispersible Tablets (25 mg, 50 mg, 100 mg, and 300 mg). However, it was later updated as requested by CHMP with the results of the Phase II Tier A studies using zonisamide, together with a comprehensive justification (including published epidemiological data) for the refined market penetration (Fpen).

Zonegran Hard Capsules (25 mg, 50 mg, 100 mg) and Zonegran Orodispersible Tablets (25 mg, 50 mg, 100 mg, 300 mg) are currently indicated as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults. An updated environmental risk assessment has been submitted with this application encompassing environmental exposure due to the current authorised indication and environmental exposure due to the planned extensions to the indication to include adjunctive use in paediatric patients (aged 6 years and above) and monotherapy in newly diagnosed adult patients.

The projected $PEC_{surfacewater}$ is 0.5 µg/L, based on the assumption of 100% market share and a refined market penetration (Fpen) value of 0.002. This worst-case refined (Fpen) value has been calculated using the highest epidemiologically-based prevalence value (0.5%) in Europe for the indication for all paediatric ages and adult patients combined.

Since using the worst-case refined Fpen based on the prevalence (as stipulated in the Questions and Answers document (EMA/CHMP/SWP/44609/2010), the $PEC_{surfacewater}$ default value of 0.01 µg/L as outlined in the NfG on Environmental Risk Assessment of Medicinal Products for Human Use (Doc. Ref. EMEA/CHMP/SWP/4447/00) has been exceeded (PEC = 1.25 µg/L), a Phase II environmental fate and effect analysis should be performed.

A comprehensive Phase II Tier A environmental fate and effects analysis was performed for zonisamide, showing that for projected $PEC_{SURFACEWATER}$ values of 0.5 µg/L (based on the assumption of 100% market share and highest prevalence rate for the indication), the environmental risk from exposure to zonisamide is negligible.

Zonisamide is well absorbed and excreted primarily in the urine as parent drug and metabolised drug. The major human metabolites have been shown to be pharmacodynamically inactive.

The adsorption coefficient (Koc) values of zonisamide in various matrices (soil, sediment) are low indicating high to very high mobility, such that an environmental assessment in the terrestrial compartment is not necessary. No results on adsorption to sludge were reported. The log K_{ow} (n-octanol/water partition coefficient) of zonisamide is low (0.510), such that there is negligible potential for bioaccumulation.

Given the high mobility and low bioaccumulation as indicated by the very low log K_{ow}, the CHMP considered the decision for not perform terrestrial compartment acceptable.

Zonisamide exhibits a spectral absorption in the range of 239 to 283 nm, which is within the solar ultraviolet (UV) range, and therefore it would be expected to undergo photodegradation in aqueous environments. An aqueous photodegradation study was performed, showing that zonisamide rapidly undergoes photodegradation over a range of pH values, with experimentally determined half-lives of 2.70, 1.78 and 1.37 hours for pH values of 5, 7 and 9 respectively. Based on the short half-lives (less

than three hours), the MAH stipulated that photodegradation is a major removal pathway for zonisamide in wastewater treatment plants and other aqueous environmental compartments

The CHMP however did not agree that the elimination/removal in wastewater treatment plants and other aqueous environmental compartments was plausible due to the observed photodegradation. In wastewater treatment plants water is not clear and therefore there is insufficient sunlight. From toxicity tests in clear water zonisamide was hardly degraded after 2-3 days.

In a GLP-compliant aerobic degradation study (OECD Guideline 308) in two non-contaminated water/sediment systems (GV = nutrient poor system with low potential for degradation; SW = small pond with higher organic content), zonisamide only partially dissipated from the water layer to the sediment layer with <10% zonisamide present in the sediment at and after 14 days. In both the water and sediment layer, zonisamide gradually degraded. Degradation products (metabolites) were found in both GV and SW systems. In the GV system, two relevant metabolite fractions (Met 1 and Met 3) and in the SW system four relevant metabolite fractions (Met 1, Met 2, Met 3 and Met 4) were detected. Met 1 was probably a degradation product of the other metabolites. The DT50 values for zonisamide in water, sediment and total system were 4 to 14 days, 4 to 21 days and 4 to 17 days respectively in SW and GV systems, with the lower DT50 values of 4 days observed in the SW system as expected. The total system DT50 values for the metabolites in the water/sediment systems were 9 to 30 days.

The CHMP noted that the data from the degradation study suggests that zonisamide only partially dissipated from the water layer to the sediment layer and gradually degraded in both layers. DT50 were determined and amounted to between 4-21 days for parent compound and 9-30 days for metabolites. Since more than 10% of the radioactivity was present in sediment at the end of the study (21% and 17% as bound residue in GV and SW sediments, respectively), the MAH is recommended to perform a toxicity study on a sediment dwelling organism (Hyalella sp; Lumbriculus sp. or Chironomus sp.) and compare this to the PECsediment.

An aquatic risk assessment, based on long-term toxicity data as well as acute toxicity test results, has demonstrated that the aquatic risk from zonisamide to surface water and ground water compartments and to microorganisms is negligible. Findings from long-term aquatic toxicity studies showed that zonisamide was non-toxic at 10 mg/L in fish and Daphnia (only one concentration tested) and at 100 mg/L in algae. The derived PEC/PNEC ratios were very low (≤0.0005) using the higher epidemiologically-based projection of $PEC_{surfacewater}$ (0.5 µg/L).

The CHMP noted that $PEC_{surfacewater}$: $PNEC_{microorganism}$ ratio was below 0.1, thus according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), no further evaluation of the fate and effects of the drug substance on micro-organisms are required.

The MAH concludes that no environmental risk is presented by zonisamide from the use of Zonegran Hard Capsules (25 mg, 50 mg, 100 mg) and Zonegran Orodispersible Tablets (25 mg, 50 mg, 100 mg, 300 mg), taking into account the indication as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults and the extension of the indication to include adjunctive use in paediatric patients (aged 6 years and above) and monotherapy in newly diagnosed adult patients.

The conclusion of the completed Phase II environmental risk assessments for zonisamide was supported by CHMP. The extension of the indication to include adjunctive use in paediatric patients (aged 6 years and above) and monotherapy in newly diagnosed adult patients and thus increase the overall environmental exposure is not thought to impact on the environmental risk.

However, the risk assessment to the sediment compartment cannot be concluded and the MAH was recommended to perform a toxicity test on a sediment dwelling organism in the first RSI.

In their answer, the MAH argued that such study was not necessary, taking into account the extremely large safety factor of more than 35,700 and the following factors:

- The NOEC of 10 mg/L (only dose tested) in a fathead minnow fish early-life stage test was the same as the NOEC (only dose tested) in the *Daphnia magna* 21-day reproduction test, showing that zonisamide is of low toxicity and that comparable lack of toxicity has been seen in these two aquatic species. As shown in the ERA for Zonegran (Zonisamide), the NOECs for fresh water algae and for activated sludge respiration inhibition were >100 mg/L also demonstrating extremely low inter-species toxicities.
- It can therefore be assumed that sediment dwelling organisms including *Hyalella sp.*, *Lumbriculus sp.* and *Chironomus sp.* will not show markedly different toxicity to zonisamide and that a very large safety factor over the $PEC_{SEDIMENT}$ will exist for sediment dwelling organisms.
- *Hyalella sp.*, *Lumbriculus sp.* or *Chironomus sp.* would have to be many times more sensitive toxicologically than the fathead minnow or *Daphnia magna* in order to trigger a requirement for further evaluation of the sediment compartment.
- Since the NOEC of 10 mg/L used for the calculation of $PNEC_{SEDIMENT}$ was the only dose tested, the true NOEC is in fact greater than 10 mg/L, such that the safety margin is actually greater than 35,700.
- The major human metabolites of zonisamide have been shown to be pharmacodynamically inactive, as outlined in the ERA for Zonegran (Zonisamide).
- Zonisamide has high mobility and low bioaccumulation potential, as outlined in the ERA for Zonegran (Zonisamide).

Even if sediment dwelling organisms were more toxicologically sensitive compared to other species and a higher assessment factor (100 or 1000 rather than 10) was used, the sediment compartment risk would remain extremely low and the $PNEC_{SEDIMENT}$ would be orders of magnitude lower than $PEC_{SEDIMENT}$ (>3570 or >357, respectively).

The CHMP considered that the algae test did not fulfill the validity criteria according to OECD 201. The algae did not grow in the first 24 h, as the test was conducted in the dark for the first 24 h. This is inacceptable. The MAH argued that the active ingredient is photolytic not stable and would be degraded, but the concentration was stable during the entire test, even after the illumination was started after 24 hours.

The data from the water/sediment-degradation study suggests that more than 10% of the radioactivity is present in sediment at the end of the study (active ingredient plus non extractable residues). Hence, the CHMP maintained its position that a study on sediment dwelling organisms (preferably with Lumbriculus variegatus) should be performed to evaluate the potential risk to sediment organisms.

2.3.2. Conclusion on non-clinical aspects

No new non-clinical data have been submitted in the application.

The MAH has provided a revised ERA including a Phase I with calculation of a $PEC_{surfacewater}$ and additional studies for a Phase II assessment.

With regards to the CHMP request to perform a toxicity test on a sediment dwelling organism, the CHMP acknowledged the MAH's response and equilbrium partitioning calculations presented. However, when both PEC and PNEC are converted to a corresponding sediment concentration using the same equations and sorption constant, the PEC/PNEC ratio remains equal. Hence, the PEC/PNEC ratio for water of 0.0005 also applies to sediment.

The MAH is therefore recommended to provide a valid algae growth inhibition test and a study on sediment dwelling organisms: the wording of section 6.6, Special precautions for disposal, is amended to "Any unused medicinal product or waste material should be disposed of in accordance with local requirements" until the evaluation of the study results warrants otherwise.

2.4. Clinical Efficacy aspects

Four studies were submitted:

- The pivotal phase III randomised controlled trial (E2090-E-44-**310**), which evaluated ZNS used as a monotherapy to treat newly diagnosed partial epilepsy in adults vs carbamazepine (CBZ), in a non-inferiority study design (The study evaluated 6- and 12-month seizure freedom), and some information on its extension study E2090-E044-**314**.
- A dose finding study for monotherapy (AN46046-**304**).
- An open label long term safety study, extension to study 304 (ELN46046-**355**).
- A phase I study to examine the effect of race on pharmacokinetics (ELN406046**-108**).

Tabular overview of clinical studies

Table 1. Overview of the studies submitted

Study	Design Patient population	Study phases	Study arms Dose	Main endpoints
Study 310 2007-2011 EU/AU/ASIA 22 countries 120 centres Monotherapy	Rd MC Db Dd AC PA Non-inferiority study Newly diagnosed epilepsy with PS ± SG 18-75 years of age	Screening: 2 weeks Titration 4 weeks Flexible dosing 36-78 weeks Maintenance 26 weeks Down titration: 6 weeks	Flexible dose ZNS OD Range 200-500 mg/day in steps of 100 mg/day (n=281) CBZ BID Range 400-1200 mg/day in steps of 200 mg/day (n=300)	Proportion of subjects seizure free for 6 months Proportion of subjects seizure free for 12 months Safety
Study 304 2002-2004 US/EU/Mexico Dose-response	Rd MC Db Dd DC PA Newly diagnosed epilepsy with CPS ± SG 16-91 years of age	Screening: 2 wks Titration/Maintenance: 40 weeks Titration 2-4 weeks: depending on dose Conversion: 2 weeks	Fixed dose ZNS OD 25 mg/day (n=56) 100 mg/day (n=52) 300 mg/day (n-59)	Time to 2nd CPS or 1st GTC-seizure Proportion of subjects seizure free for 6 months Retention rates for duration of the study Safety
Study 314	Blind till unblinding of	Duration undefined	ZNS (n=137)	Safety

Extension of study 310 Safety/efficacy	study 310 Ongoing	Data cut off of deblinding 24-02-2011	CZP (n=158)	Seizure control
Study 355 2003-2005 EST/LT/Ukraine. Extension of study 310 Safety/efficacy	Open label Uncontrolled Patients who completed study 304 and with seizure control	~24 months Starting dose 100 mg/day Titration up to 300 mg/day	ZNS 100 mg/day (n=20) 300 mg/day (n=12)	Safety Seizure control

Legend

AC=active controlled, BID=Twice a day, CBZ=carbamazepine, CPS=complex partial seizures, Db=double-blind, DC=dose-controlled, Dd=double-dummy, GTC=Generalised tonic-clonic seizures, MC=multicenter, OD once a day, , PA=parallel group, PS=partial seizures, Rd=randomized, ZNS=Zonisamide

2.4.1. Pharmacokinetics

One clinical pharmacology study, study 108, is included in this submission. This study evaluated the effect of race on single-dose pharmacokinetics (PK) of zonisamide in healthy White, Black, and Asian subjects. The results of the study showed that the pharmacokinetics of zonisamide (100 mg single dose) are not influenced by race.

The CHMP agreed with these conclusions. Cmax was marginally higher in Asians and African descendants compared to Caucasian, but as zonisamide is gradually titrated based on individual response, it is not expected that this marginal difference will be of clinical relevance.

2.4.2. Clinical efficacy

To support the clinical efficacy of the monotherapy claim two studies were submitted: the dose finding study (AN46046-304) and the pivotal phase III randomised controlled trial (E2090-E-44-310).

Dose-response study: AN46046-304

Study 304 was a Phase 3, multicenter, double-blind, randomized study in 169 adult subjects with newly diagnosed epilepsy and complex partial seizures, conducted to evaluate 3 dose levels of ZNS (25, 100, and 300 mg/d) as monotherapy in adult subjects with newly diagnosed epilepsy and complex partial seizures. The study was conducted in 34 centres between 20 February 2002 and 20 October 2004 in the US, Europe, and Mexico. A new diagnosis of epilepsy meant a subject for whom this was the first diagnosis of epilepsy, or a subject who had a previous diagnosis of epilepsy but had not received AED therapy for that previous diagnosis for at least 2 years.

The initial zonisamide dose was 25 mg/day or 50 mg/day. Patients in the 100- and 300-mg/day group were up-titrated with 50 mg weekly until the target dose was reached. If a subject could not achieve the target dose because of tolerability issues, the subject was discontinued from the study.

The efficacy evaluation period was the double-blind titration and treatment phase of 40 weeks.

Primary endpoint was the time to exit, defined as time from first dose of study drug to exit from study due to occurrence of two complex partial seizures or one generalized tonic-clonic seizure. Secondary endpoints concerned the proportion of subjects seizure-free for at least 6 months and the proportion of subjects remaining on treatment for the duration of the study.

The primary efficacy analysis and the secondary efficacy analysis of 6 month-seizure freedom were performed on the safety population (all those randomised who received at least one dose of the study drug). The following tables summarise the efficacy results from the study.

Table 2. Time to Predefined Exit Criterion (2 Complex Partial Seizures or 1 Generalized Tonic-Clonic Seizure) (Safety Population)

The percentage of subjects who reached a predefined exit criterion was lower in the 300-mg/day group (22.0%) than in the 25- and 100-mg/day groups (41.1% and 40.4%, respectively). However, this difference was not statistically significant in the safety population. This raises the possibility that the study was underpowered, although there was a trend (p value 0.060).

	Zonisamide		
	25 mg/day (N=56)	100 mg/day (N=52)	300 mg/day (N=59)
Number of subjects who reached exit criterion [n (%)]	23 (41.1)	21 (40.4)	13 (22.0)
Time (days) to reach exit criterion, percentile[a]			
25th (95% CI)	84.0 (49.0, 168.0)	74.0 (36.0, 185.0)	266.0 (162.0, NE)
50th (95% CI)	NE (162.0, NE)	NE (161.0, NE)	NE
75th (95% CI)	NE	NE	NE
Comparison to zonisamide 300 mg/day[b]			
Risk ratio (95% CI)	1.92 (0.97, 3.79)	2.07 (1.04, 4.14)	
Comparison to zonisamide 100 mg/day[b]			
Risk ratio (95% CI)	0.93 (0.51, 1.67)		
p-value (linear)[b]	0.060		
p-value (quadratic)[b]	0.148		

CI = confidence interval; NE = not estimable.

a Results are based on the Kaplan-Meier method.

b The risk ratio, 95% CI for risk ratio, and p-value are based on Cox proportional hazards regression model under the assumption that the dosing groups were equally spaced.

Table 3. Proportion of Subjects Seizure-Free for at Least 6 Months (Safety Population)

The percentage of subjects who remained seizure-free for at least 6 months was higher in the 300-mg/day group (50.8%) than in the 25- and 100-mg/day groups (33.9% and 30.8%, respectively). However, these differences were not statistically significant (p=0.061). The difference seems to apply only to those subjects with a history of generalized tonic-clonic seizures, for whom the proportion of subjects seizure-free for at least 6 months was 60.0% in the 300-mg/day group, as compared to 30.8% and 33.3% in the 25- and 100-mg/day groups, respectively. There was essentially no difference across treatment groups in those with a history of complex partial seizures.

	Zonisamide			p-value[a]
	25 mg/day (N=56)	100 mg/day (N=52)	300 mg/day (N=59)	
Number of subjects [n (%)]	19 (33.9)	16 (30.8)	30 (50.8)	0.061
95% confidence interval for proportions	21.81, 47.81	18.72, 45.10	37.5, 64.11	
Comparison to zonisamide 300 mg/day[b]	0.067	0.032		
Comparison to zonisamide 100 mg/day[b]	0.726			
Seizure history: complex partial	N= 39	N= 33	N= 35	
Number of subjects [n (%)]	13 (33.3)	10 (30.3)	12 (34.3)	
95% confidence interval for proportions	19.09, 50.22	15.59, 48.71	19.13, 52.21	
Seizure history: generalized tonic-clonic	N= 26	N= 27	N= 35	
Number of subjects [n (%)]	8 (30.8)	9 (33.3)	21 (60.0)	
95% confidence interval for proportions	14.33, 51.79	16.52, 53.96	42.11, 76.13	

a The p-value for trend is based on the Cochran-Mantel-Haenszel statistic under the assumption that the dosing groups were equally spaced.

b The p-value for treatment comparisons is based on the Pearson's Chi square statistic.

Table 4. Proportion of Subjects Remaining on Treatment for the Duration of the Study (Safety Population)

The proportion of subjects who remained on treatment for the duration of the study was similar in all treatment groups: 41.1% in the 25-mg/day group, 40.4% in the 100-mg/day group, and 40.7% in the 300-mg/day group.

	Zonisamide			
	25 mg/day (N=56)	100 mg/day (N=52)	300 mg/day (N=59)	p-value[a]
Number of subjects [n (%)]	23 (41.1)	21 (40.4)	24 (40.7)	0.967
95% confidence interval for proportions	28.10, 55.02	27.01, 54.90	28.07, 54.25	
Comparison to zonisamide 300 mg/day[b]	0.966	0.975		
Comparison to zonisamide 100 mg/day[b]	0.942			
Seizure history: complex partial	N= 39	N= 33	N= 35	
Number of subjects [n (%)]	17 (43.6)	15 (45.5)	11 (31.4)	
95% confidence interval for proportions	27.81, 60.38	28.11, 63.65	16.85, 49.29	
Seizure history: generalized tonic-clonic	N= 26	N= 27	N= 35	
Number of subjects [n (%)]	11 (42.3)	8 (29.6)	18 (51.4)	
95% confidence interval for proportions	23.35, 63.08	13.75, 50.18	33.99, 68.62	

a The p-value for trend is based on the Cochran-Mantel-Haenszel statistic under the assumption that the dosing groups were equally spaced.

b The p-value for treatment comparisons is based on the Pearson's Chi square statistic.

The proportion reaching an exit criterion was lowest for the 300mg dose (22% v 40.4% for the 100mg dose and 41.1% for the 25mg dose). However these differences were not statistically significant. Results for the 25 mg and 100mg group are almost the same. In addition, it appears that a higher percentage of women met an exit criterion in all 3 treatment groups.

The proportion of subjects seizure-free for at least 6 months was the highest in the 300mg treatment group (50.8% v 33.3% for the 100mg group and 30.8% for the 25mg group). Again this difference was not statistically significant. Even though statistical significance was not achieved for 6 month seizure freedom it is clear that results in the 300mg group are considerably higher than those for the 100mg and 25 mg groups which are broadly similar.

There was no difference in outcome for 6 month seizure freedom in those with a history of complex partial seizures.

Withdrawals for any reason were the highest for the 300mg group. This study also showed a higher proportion of females meeting an exit criterion, however modelling the effect of gender showed no evidence of a gender treatment interaction and the CHMP concluded that the response to ZNS does not seem to be affected by gender.

Despite not showing statistical significance when compared to 25mg or 100mg doses a monotherapy dose of 300mg appears reasonable given that lower rates for achieving an exit criterion and higher 6 month seizure free rates were associated with the 300mg dose and that doses of 300 to 500mg are already approved for Zonegran in the adjunctive setting.

Main clinical study: E2090-E-44-310

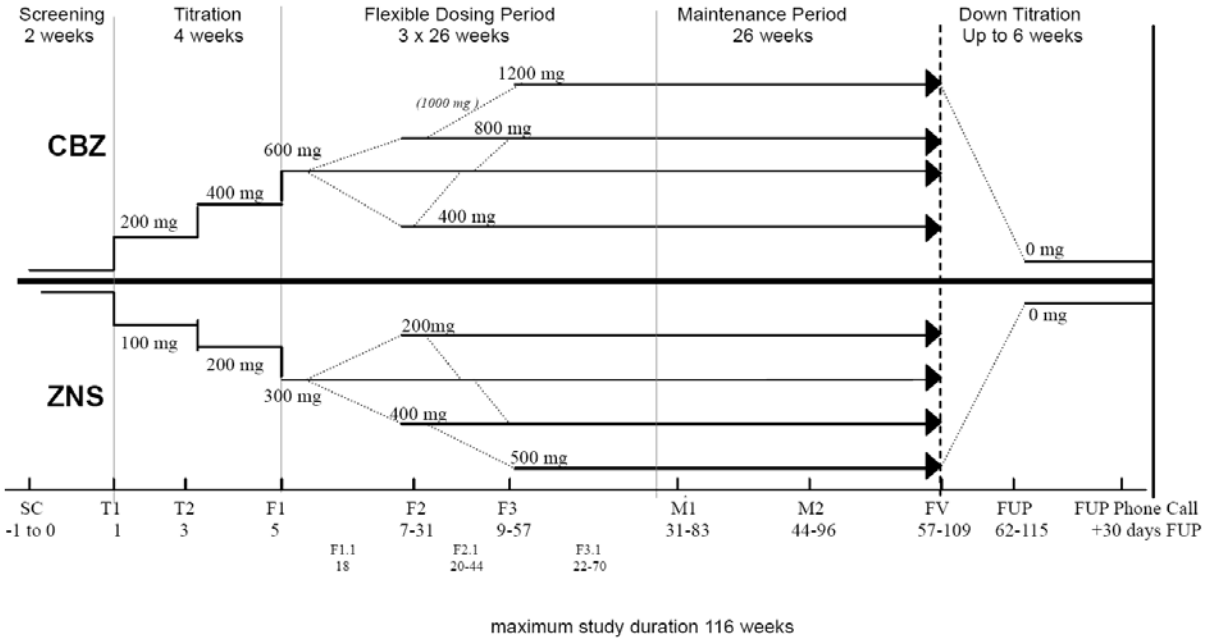
Study 310 was a Phase III, multicenter, randomized, double-blind, non-inferiority study comparing zonisamide (ZNS) against Tegretol Retard (a prolonged release formulation of carbamazepine, referred to as CBZ in this document), using a flexible dosing regimen. The study was conducted in 583 adult subjects with newly diagnosed partial onset seizures with or without secondary generalized tonic-clonic

seizures, in Europe, South Africa, Australia, and Asia. Subjects were randomized to a target dose of CBZ 600 to 1200 mg/d (twice daily) or ZNS 300 to 500 mg/d once daily, and received treatment for up to 24 months, depending on response. During the Flexible Dosing Period, one down-titration step to 200 mg/d ZNS or 400 mg/d CBZ was permitted in case of intolerability.

The primary objective was to assess the efficacy of ZNS compared to CBZ when given as monotherapy to newly diagnosed subjects with partial seizures by assessment of 26-week seizure free rate.

Secondary objectives included assessment of the efficacy of ZNS compared to CBZat one year assessment of safety and tolerability of ZNS compared to CBZ and assessment of the quality of life of subjects taking ZNS compared to CBZ.

Figure 1. The study phases with dosage schedule



During the Titration Period, the starting dose was 100 mg/day ZNS or 200 mg/day CBZ. The dose was increased every 2 weeks until a dose of 300 mg/day ZNS or 600 mg/day CBZ was reached.

Subjects who were unable to achieve the target dose of 300 mg/day ZNS or 600 mg/day CBZ were either withdrawn or in case of intolerance permitted one down-titration step during the first 2 weeks of the flexible dosing period (FDP). If subjects consequently experienced a seizure, their dose could be up-titrated provided their AE had resolved. A maximum of two up-titrations were allowed for these subjects up to a maximum dose of 400 mg/day ZNS or 800 mg/day CBZ.

During the FDP the need for up- or down-titration was evaluated based on the occurrence of seizures and adverse events. Subjects could be withdrawn from the study if they experienced seizures during the FDP.

Subjects who were seizure-free for 26 weeks in the FDP entered the maintenance period and continued on a stable dose for a further 26 weeks. Subjects who experienced a seizure during the maintenance period were withdrawn from the study.

Subjects who completed the study (seizure-free for 26 weeks during the Maintenance Period) could continue ZNS/CBZ treatment in extension study or were withdrawn from the study. Study medication was down-titrated at a rate of 100 mg/week ZNS or 200 mg/week CBZ.

Endpoints

The primary efficacy endpoint was the proportion of subjects seizure-free for 26 weeks as assessed via the occurrence of seizures as documented in the seizure diary. For the primary efficacy analysis, a subject was classified as having achieved a 26-week seizure-free period if they were free of all seizures, regardless of seizure type, for 26 weeks while receiving the same dose.

The key secondary efficacy endpoint was the proportion of subjects seizure-free for at least a 12-month. Other secondary efficacy variables included the time to withdrawal due to lack of efficacy/AE, time to the end of a 26-week and 52-week seizure-free period.

Sample Size and Power Considerations

The sample size was based on the primary efficacy endpoint of proportion of subjects seizure-free for at least 6 months. The non-inferiority margin (delta) is a relative 20% difference (e.g., an absolute difference of 12% if proportion seizure-free is 60%) up to a maximum of an absolute 12% difference.

Assuming that the proportion seizure-free in the ZNS and CBZ groups is 60%, 262 subjects per group were required to conclude that ZNS is noninferior to CBZ if the lower limit of the 95% CI of the treatment difference (CBZ – ZNS) is above –12% with 80% power and a 1-sided 0.025 alpha level. If the proportion of seizure-free subjects in both groups is 65% or 70%, then 262 subjects per group would provide 82% and 85% power, respectively.

Allowing for a 10% drop-out rate, a total of 582 subjects were to be randomized in a ratio of 1:1 between ZNS:CBZ.

Analysis

The primary analysis was performed in the per-protocol population. The PP population was defined as the subset of the ITT Population who had no major protocol violations or deviations.

A sensitivity analysis was performed in the ITT population. The ITT population was defined as defined as all randomized subjects who received at least one dose of study medication.

The primary analysis presented the difference in the proportion of subjects seizure-free for at least a six month (26 week) period between the two groups with a lower 95% confidence limit. Subjects were classified as having achieved a 6-month (26-week) seizure-free period if they were free of all seizures, regardless of seizure type, for 182 days receiving the same dose.

All 581 treated subjects were included in the safety and ITT populations. For seizure-free endpoints in the ITT analyses, a subject with missing seizure data was assumed not to be seizure-free at that visit. If a subject dropped out before the end of the assessment period, they were considered not seizure-free for that endpoint.

No interim analysis was planned/conducted.

Overall comments on Methods

Study 310 was largely in line with the recommendation made for monotherapy studies in the Note for Guidance on Treatment of Epileptic Disorders (CPMP/EWP/566/98 rev 1). The company also adapted the study design in accordance to the scientific advice given e.g. dosage schedule of CBZ, extension of the maintenance phase to 12 month.

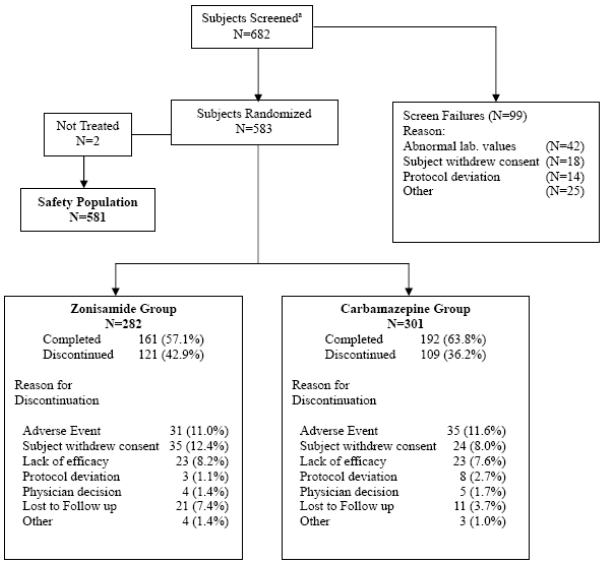
It is noted that, as monotherapy studies in epilepsy only include an active control, assay sensitivity may be an inherent problem (see discussion on efficacy).

In the context the known efficacy of ZNS in the add-on setting a single positive trial in monotherapy was considered sufficient.

Population and baseline characteristics

A total of 682 subjects were screened, 99 of which were excluded. Of the 583 subjects randomised 2 were not treated.

Subject disposition



There were higher discontinuation rates for Zonisamide than Carbamazepine, although the discontinuations due to adverse events and lack of efficacy were the same between the two active treatments.

127 out of 583 (21%) subjects were excluded from the PP population. The most common reasons for exclusion were subjects not being up-titrated according to protocol requirements following a seizure, missing seizure diaries during the FDP, and < 80% compliance. There were no obvious differences in reasons for exclusion between the treatment groups.

Mean age, height, weight, BMI and distribution of gender were similar in both treatment groups.

Baseline characteristics related to epilepsy were broadly similar. The mean number of fits in the 12 months prior to randomisation was similar in both treatment groups as was prior medication use. A slightly higher proportion of those in the CBZ group (15.3% v 13.2%) had taken a prior AED or nervous system drug. Phenytoin was the most widely used AED in both groups.

Results

Main outcomes study 310

	ZNS	**CBZ**		
n-ITT n-per protocol	281 223	300 233	Diff	$CI_{95\%}$
Six months seizure freedom PP-population	**79.4%**	**83.7%**	**-4.5%**	**-12.2% ; 3.1%**

	ZNS	CBZ		
ITT-population	**69.4%**	**74.7%**	**-6.1%**	**-13.6% ; 1.4%**
Twelve months seizure freedom				
PP-population	67.6%	74.7%	-7.9%	-17.2% ; 1.5%
ITT-population	55.9%	62.2%	-7.7%	- 16.1% ; 0.7%
Sensitivity analysis six months seizure freedom (PPP)				
Excluding country	79.4%	83.7%	-4.3%	-11.4% ; 2.8%
Adjusted for pre-treatment seizures			-4.2%	-11.8% ; 3.4%
By seizure type				
All partial	76.4%	86.0%	-9.6%	-19.2% ; 0.0%
Simple partial	72.3%	75.0%	-2.7%	-20.0% ; 14.7%
Complex partial	76.9%	93.0%	-16.1%	-26.3% ; -5.9%
All generalized Tonic-Clonic	78.9%	81.6%		-11.5% ; 6.0%
Secondary TC	77.4%	80.0%	-2.6%	-12.4% ; 7.1%
Generalized Tonic-Clonic	85.7%	92.0%	-6.3%	-23.1% ; 10.5%
Time to 12 month seizure freedom				
PP-population	381	381	0.88	0.70 ; 1.11
ITT-population	382	381	0.83	0.67 ; 1.04

Legend

CBZ=carbamazepine , CI95% = 95% confidence interval, Diff=Difference ITT=Intention To Treat population, HR=Hazard ratio, LOE=lack of efficacy, NC= = Not calculable, PPP =Per Protocol Population, ZNS= zonisamide; CBZ=carbamazepine

Quality of life measures and neuropsychological evaluations

Aldenkamp–Baker Neuropsychological Assessment Scale

There were no clinically or statistically significant differences in ABNAS scores between the groups for any of the parameters.

Bond–Lader Scale

Analysis of Bond–Lader mood assessment scale data for the ITT Population for observed cases (OC) and last observation carried forward (LOCF) showed a statistically significant difference between the groups in favour of CBZ for dysphoria.

Quality of Life in Epilepsy – Problems

There was no statistically significant difference between the groups for overall score in QOLIE-31-P.

Short Form 36 Health and Wellbeing questionnaire

There was no statistically significant difference between the groups for aggregate physical component score and aggregate mental component score.

Except for mental health at the FV/ETV (ZNS, 0.54 vs CBZ, 2.56; $P = 0.0328$), no statistically significant differences between treatment groups were observed.

European Quality of Life Group 5-Dimension Self-Report Questionnaire

There were no clinically significant differences in EQ-5D scores between the groups. EQ-5D health state tariff scores were similar between treatment groups.

2.4.3. Clinical studies in special populations

No efficacy studies were carried out in special populations

2.4.4. Analysis performed across trials (pooled analyses AND meta-analysis)

No pooled analyses or meta-analysis has been presented

2.4.5. Discussion on clinical efficacy

There is no guidance on appropriate inferiority margins to be used: the *Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders* states that "The non-inferiority margin will need to be justified by the applicant", and this has to be done on the basis of a clinically important difference in efficacy.

Following the Scientific Advice, the MAH chose an absolute inferiority margin of 12%, based on an expected efficacy of 60% from CBZ and a relative difference in efficacy between CBZ and ZNS of ≤20%, with the latter being based on ILAE guidance on rating studies to be used for evidence based guidelines of AEDs in initial monotherapy. No inferiority margin was set for the secondary efficacy variable of 52 week seizure freedom.

In the pivotal study (310) Zonisamide was marginally (12.2%) outside the pre-specified inferiority margin of 12%. Carbamazepine efficacy as measured by the proportion of subjects seizure free for six months in the per-protocol population was unexpectedly high (83.7%). Likewise efficacy rates for zonisamide were also high, at 79.4%. This raised the question whether this might indicate that the population included was not at a high risk for seizures.

The MAH was therefore asked to justify that the enrolled population was sufficiently at risk to enable finding differences between zonisamide and carbamazepine, if any, but also between these two products and placebo, if there had been one.

The MAH provided evidence to demonstrate that the population studied in Study 310 was sensitive for seizures: patients included were at risk of recurrence given their baseline seizures, inclusion criteria of EEG abnormalities; moreover 25-30% of the patients in the study experienced at least one seizure in the double-blind phase.

Median number of seizures pre-randomisation

The median number of seizures in the year prior to randomization was similar for the Study 310 population and other published trial populations, and varied from 3 to 4. In terms of design and efficacy endpoints the studies Brodie et al 2007 and Kwan et al 2001 are the most similar trials to the Zonisamide monotherapy RCT. The median number of seizures in the Kwan trial is 3 in both arms. In the Brodie 2007 trial subjects in carbamazepine arm had a median number of 3 seizures and those in the levetiracetam arm had 4. This is similar to the median number of seizures experienced by participants in both arms of the zonisamide monotherapy trial.

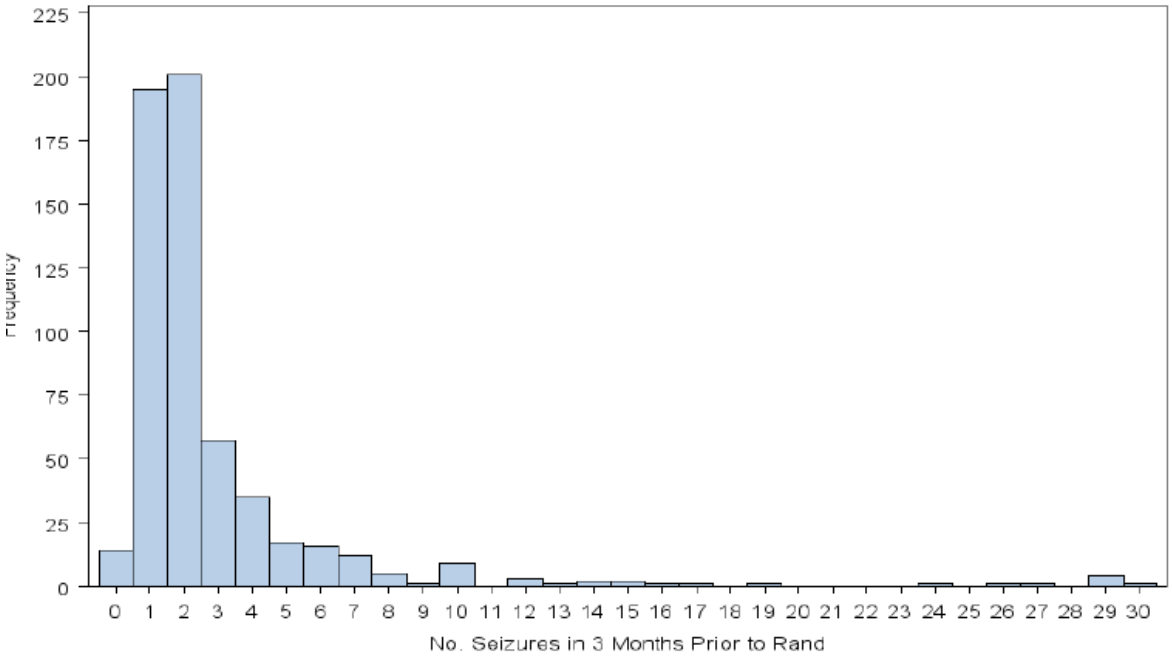
Based on literature (Hauser et al., 1998; Kim et al., 2006; Marson et al., 2008) patients in study 310 were at a high risk for recurrence within 12 months: patients with two single unprovoked seizures had a risk of recurrence of a third seizure of 76%, with a median time to recurrence of 4.5 months (Hauser 1998). Risk factors for recurrence included presence of a neurological disorder, abnormal EEG, and number of seizures pre-randomisation (Kim 2006). Based on this, patients in study 310 would be classified at risk of recurrence (>= 2 seizures, EEG abnormalities). The probability of recurrence after 1 year was 59% for the immediate treatment group and 67% for the delayed treatment group (Kim 2006).

The CHMP accepted that the inclusion criteria for Study 310, Kwan et al 2011 and Brodie et al 2007 were similar, so all three study populations should be at reasonably similar risk of seizures although a lower risk may occur by chance. The CHMP also agreed that in general clinical practice patients experiencing 2 partial seizures with confirmatory EEG evidence are started on an AED as monotherapy. Also, in study 310, patients were shown to be at high risk for recurrence within 12 months, which indicates that a population sensitive for seizures was included.

A simulation of the expected number of seizures was performed, based on the seizure distribution at 3 months and 12 months prior to the start of ZNS/CZB and under different assumptions of treatment efficacy.

The results of the simulation (based on seizure distribution in the 12 and 3 months prior to randomisation) showed that the actual mean number of seizures experienced over 156 days in the study was approximately 20% of that which would be expected based on baseline seizure frequency in an untreated population.

Figure: number of seizures in the three months prior to randomization, ITT population



Note: For orientation 14 subjects rep ort 0 seizures (first column). Hence columns larger than colomn 1 indicate > 14 subjects a and those less higher than 14 subjects.

The table below show the results of the simulations assuming zonisamide is 10 and 20% less efficacious than carbamazepine for varying levels of assumed seizure reduction and in the assumption of a 30% withdrawal rate.

Summary of results of simulations using alpha =0.25, beta=4.7 and assuming 30% withdrawals

Assumed reduction in baseline seizure frequency		Number Seizures in 176 days				Overall % responders: 176 days seizure freedom		Mean Treatment difference in response	Observed 95% simulation interval for treatment difference *
ZNS	CBZ	ZNS Mean	ZNS Var	CBZ Mean	CBZ Var	ZNS	CBZ	ZNS-CBZ	
45%	50%	2.56	7.44	2.33	6.36	34.8	37.8	-0.030	-0.108, 0.047
40%	50%	2.79	8.60	2.33	6.36	32.2	37.8	-0.056	-0.134, 0.021
54%	60%	2.14	5.56	1.86	4.45	40.5	45.0	-0.045	-0.126, 0.037
48%	60%	2.42	6.79	1.86	4.44	36.6	45.0	-0.084	-0.166, -0.002
63%	70%	1.72	3.93	1.39	2.85	47.5	54.1	-0.067	-0.147, 0.016
56%	70%	2.05	5.16	1.39	2.85	41.9	54.1	-0.122	-0.202, -0.040
72%	80%	1.30	2.58	0.93	1.58	56.2	65.7	-0.095	-0.174, -0.016
64%	80%	1.67	3.78	0.93	1.57	48.3	65.7	-0.174	-0.251, -0.096
81%	90%	0.88	1.46	0.46	0.63	67.0	79.5	-0.125	-0.198, -0.051
72%	90%	1.30	2.57	0.47	0.63	56.2	79.5	-0.233	-0.307, -0.159

The simulation demonstrates that the actual mean number of seizures experienced over 156 days in the study is approximately 20% of that which would be expected in an untreated population. However it is unclear whether the model assumes that the risk of a further seizure remains similar regardless of how many previous seizures a study subject has experienced. This assumption may have been optimistic, but it is unlikely that a regression to the mean should result in such a reduction. This simulation provides some evidence that the population could be considered not to be at low risk of seizures.

The observed treatment difference of -6.1% in Study 310 was contained within all simulation intervals when (95%) where the efficacy of the two drugs were equal and ranged between 50 and 80%.

The simulation using assumptions about difference in efficacy with and without withdrawals showed that where CBZ was assumed to be 10% more efficacious than ZNS and there were no withdrawals modelled efficacy rates were similar to those noted for the primary efficacy endpoint in Study 310. However when the model included a withdrawal rate of 30%, similar to that in Study 310, modelled efficacy rates were lower.

Response rate by baseline seizure frequency

Data from the 12 months baseline period indicate similar response rate irrespective of baseline seizure frequency with both treatment groups (ZNS: < 4 seizures 70.8%, > 4 seizures 65.2%; CBZ < 4 seizures 74.1%, > 4 seizures 76.4%). Data from the 3 month baseline period indicate a lower response rate in ZNS treated patients with more than 4 seizures compared the CBZ treated patients. (ZNS: < 4 seizures 71.7%, > 4 seizures 52.9%; CBZ < 4 seizures 75.7%, > 4 seizures 68.9%).

Results for the 12 months seizure freedom indicate a lower response rate in patients with more than 4 seizures for both treatments. However this is not clinically unexpected in this more difficult to treat population and seizure freedom response rates remain relatively high (ZNS and CBZ combined total: < 4 seizures 60%, > 4 seizures 56.7% from the 12 month baseline period and < 4 seizures 61.2%, > 4 seizures 46.8% from the 3 month baseline period respectively).

Differences in dosing schedules for CBZ between study 310 and Brodie, 2007

It was noted that the response rates in study 310 were higher than the ones expected based on published literature. The higher initial dosing of CBZ may account for the higher response rate under

CBZ in Study 310 compared to Brodie 2007 (83.7% v 73% in the PP population and 74.7% v 66.7% in the ITT population). The initial doses post titration for CBZ were 400mg/day Brodie 2007 and 600mg/day Study 310. In addition to this there were also other differences e.g. the titration period for Brodie was 2 weeks as opposed to 4 weeks for the zonisamide trial.

It could be the case that the superior efficacy seen for CBZ in study 310 could be due to the different initial doses post titration, however in both studies subjects experiencing a seizure could have their doses of CBZ up-titrated (to 800mg following the first seizure and 1200mg following the second seizure) in both trials and the maximum dose for CBZ (1200mg) was similar in both trials.

Table: CBZ 6-Months Seizure Freedom by Dose from Brodie et al., 2007 and Study 310 (Per Protocol Population)

	Overall 6-month seizure freedom %				
CBZ mg dose		400 mg %	600 mg %	800 mg %	1200 mg %
Brodie 2007 6-months seizure freedom %	72,8	62,1	N/A	69,8	72,8
				gain 7,7%	
Study 310 6-months seizure freedom %	83,7	1	75,2	82,5	83,7
				gain 7,3%	

These data from Study 310 and Brodie et al., 2007 study support the concept that higher doses of CBZ will result in higher proportion of patients achieving 6 months seizure freedom. This is also supported by the general concept of dose-response proportionality observed with CBZ (Kwan et al., 2001).

Size of effect

The 6 month seizure freedom rate in the primary analysis PP population was 79.4% for zonisamide and 83.7% for carbamazepine. The adjusted absolute difference was -4.5% with 95% CIs of -12.2% and 3.1% . The lower limit for the 95% CI for the relative difference was -14.7% which was within the margin of 20%.

The difference was larger in the ITT population, 69.4% for zonisamide and 74.7% for carbamazepine. The adjusted absolute difference was -6.1% with 95% confidence intervals of 13.6% and 1.4%. The lower CI for relative difference was -18% which was within the 20% margin set for relative difference.

The difference between treatment groups was evident in the secondary analysis of 52 week seizure freedom rate in both the PP and ITT population (67.6% for zonisamide and 74.7% for carbamazepine with an adjusted absolute difference of -7.9%).

The analyses by seizure history type were pre-planned, but were exploratory in nature and hence it was not possible to exclude that the high response rate to CBZ in the complex partial (CP) subgroup may be a spurious finding. The distribution of seizure types at the time of randomization was similar between treatment groups, although there was no stratification, and the analysis of 6-month seizure freedom rates by seizure type also demonstrated similar results across treatments. However, 93% of subjects with CP seizures at diagnosis responded to CBZ vs. 77% on ZNS.

Subjects with complex seizures are more likely to develop secondary generalised tonic-clonic seizures. In this sub-group the adjusted difference in efficacy for ZNS and CBZ is 2.6% in favour of CBZ with

95% CI of -12.4% to 7.1%. Given that those with secondary generalisation, a more severe form of the disease (many of whom would have also had complex seizures) had similar response rates for ZNS and CBZ it is reasonable to assume that the large differences in efficacy noted in complex seizures could be due to chance.

Hence whether the finding in complex partial seizures (CPS) is spurious or real remains uncertain, although there are indications that this is a spurious finding. Even if real, a lesser seizure control for CPS would not worsen the prognosis, as CPS are not a grand mal, and a partial seizure neither primes a patient to a second seizure nor to refractoriness to treatment. In this sense, there is no risk of irreversible harm.

2.5. Clinical Safety aspects

2.5.1. Methods – analysis of data submitted

To support the clinical safety of the monotherapy claim data from 4 studies were submitted:

- the dose finding study (AN46046-304) and its open label long term safety study (ELN46046-355)
- the pivotal phase III randomised controlled trial (E2090-E-44-310) and its extension study (E2090-E044-314).

Study ELN46046-355 only recruited 32 participants and provides very limited information since the study was terminated by the Sponsor upon receipt of market authorization for Zonegran in the EU. Study 314 was ongoing at the time of submission therefore only preliminary, unaudited summary adverse event (AE) data for deaths, serious adverse events (SAEs), and discontinuations due to AEs are provided herein up to a cut-off date of 31 Dec 2010. Therefore the assessment is mainly focussed on studies 304 and 310.

2.5.2. Patient exposure

For study 304 a total of 167 subjects were included in the safety population (25mg, 56: 100mg, 52 and: 300mg, 59).

For study 310 a total of 581 (ZNS, 281: CBZ, 300) subjects were included in the safety population. Time on trial and mean duration of exposure was similar in each treatment group. The maximum duration was 799 days for the ZNS group and 656 days for the CBZ group.

2.5.3. Adverse events

Table 6.Overview of Adverse Events, Treatment-related Adverse Events, Deaths, Serious Adverse Events, Adverse Events Leading to Discontinuation and adverse events > 2% studies 310/304

	Study 310		**Study 304**			**Study 355**	
	ZNS n=281	**CBZ n=300**	**ZNS 25 mg/d n=56**	**ZNS 100 mg/d n=52**	**ZNS 300 mg/d n=59**	**ZNS 100 mg/d n=12**	**ZNS 300 mg/d n=20**
Any TEAE	60.5%	61.7%	89.3%	90.4%	91.5%	80%	100%
Any treatment-related	36.3%	38.3%	41.1%	44.2%	52.5%		
Maximum severity							
Mild or moderate	–	–	3.6%	3.8%	5.1%		
Mild	33.1%	34.3%	–	–	–		
Moderate	21.4%	21.7%	–	–	–		
Severe	6.0%	5.7%	0.0%	1.9%	3.4%		

Table 6.Overview of Adverse Events, Treatment-related Adverse Events, Deaths, Serious Adverse Events, Adverse Events Leading to Discontinuation and adverse events > 2% studies 310/304

	Study 310		Study 304			Study 355	
	ZNS n=281	CBZ n=300	ZNS 25 mg/d n=56	ZNS 100 mg/d n=52	ZNS 300 mg/d n=59	ZNS 100 mg/d n=12	ZNS 300 mg/d n=20
Deaths	0.4%	0.0%	0.0%	0.0%	1.7%		
Serous adverse events	5.0%	5.7%	3.6%	5.8%	6.8%		
Withdrawals due to AEs	11.0%	11.7%	5.4%	9.6%	13.6%		
AEs > 2%							
Body as a Whole			**67.9%**	**76.9%**	**67.8%**		
headache			41.1%	46.2%	47.5%		
infection			16.1%	21.2%	16.9%		
asthenia			19.6%	11.5%	11.9%		
abdominal pain			8.9%	11.5%	15.3%		
pain			14.3%	7.7%	5.1%		
flu syndrome			10.7%	11.5%	3.4%		
back pain			7.1%	7.7%	8.5%		
accidental injury			7.1%	7.7%	5.1%		
chest pain			5.4%	5.8%	5.1%		
viral infection			1.8%	3.8%	8.5%		
fever			5.4%	3.8%	1.7%		
Nervous System Disorders	**25.6%**	**29.3%**	**42.9%**	**46.2%**	**54.2%**		
headache	10.3%	12.3%				30.0%	33.%
somnolence	6.0%	7.7%	7.1%	1.9%	20.3%		
dizziness	3.9%	7.7%	12.5%	23.1%	15.3%		
memory impairment	2.8%	2.7%					
nervousness			8.9%	5.8%	5.1%		
confusion			8.9%	0.0%	6.8%		
emotional ability			3.6%	3.8%	5.1%		
paresthesia							
speech disorder			3.6%	1.9%	6.8%		
tremor			7.1%	0.0%	5.1%		
thinking abnormal			1.8%	1.9%	6.8%		
convulsion			5.4%	1.9%	1.7%		
ataxia			3.6%	1.9%	1.7%		
paresthesia	2.1%	1.0%	3.6%	0.0%	8.5%		
Musculoskeletal			**7.1%**	**9.6%**	**5.1%**		
arthralgia			3.6%	3.8%	1.7%		
disturbance in attention	2.1%	0.7%					
Gastrointestinal disorders	**19.2%**	**17.3%**	**39.3%**	**44.2%**	**40.7%**		
nausea	3.9%	3.3%	19.6%	23.1%	22.0%		
diarrhea	3.6%	3.0%	5.4%	17.3%	8.5%		
constipation	2.5%	2.3%	1.8%	0.0%	5.1%		
vomiting	2.1%	2.7%	7.1%	5.8%	3.4%		
anorexia			10.7%	11.5%	8.5%		
dyspepsia			1.8%	1.9%	3.4%		

Table 6.Overview of Adverse Events, Treatment-related Adverse Events, Deaths, Serious Adverse Events, Adverse Events Leading to Discontinuation and adverse events > 2% studies 310/304

	Study 310		Study 304			Study 355	
	ZNS n=281	CBZ n=300	ZNS 25 mg/d n=56	ZNS 100 mg/d n=52	ZNS 300 mg/d n=59	ZNS 100 mg/d n=12	ZNS 300 mg/d n=20
General disorders and administration site conditions	**12.8%**	**16.7%**					
fatigue	4.6%	4.0%					
pyrexia	3.9%	4.0%					
asthenia	1.8%	2.3%					
irritability	2.5%	0.3%					
Respiratory			**28.6%**	**23.1%**	**30.5%**		
rhinitis			12.5%	17.3%	15.3%		
pharyngitis			16.1%	7.7%	11.9%		
cough increased			5.4%	5.8%	3.4%		
sinusitis			7.1%	0.0%	5.1%		
dyspnea			1.8%	0.0%	6.8%		
bronchitis			1.8%	1.9%	3.4%		
Infections and Infestations	**13.2%**	**15.7%**				65.0%	66.7%
nasopharyngitis	3.6%	2.0%				15.0%	66.7%
upper respiratory tract infection	2.1%	2.0%					
urinary tract infection	1.1%	2.3%					
Skin and subcutaneous tissue disorders	**7.5%**	**12.7%**	**16.1%**	**11.5%**	**15.3%**		
rash	2.1%	4.3%	1.8%	3.8%	3.4%		
sweating			3.6%	1.9%	5.1%		
pruritus			1.8%	1.9%	3.4%		
Investigations	**11.7%**	**8.0%**					
weight decreased	6.8%	0.0%					
alanine aminotransferase increased	1.1%	2.0%					
Psychiatric disorders	**9.3%**	**4.7%**					
depression	2.1%	1.7%	5.4%	7.7%	6.8%		
insomnia	2.1%	0.3%	7.1%	11.5%	15.3%	20.0%	25.%
Metabolism and nutrition disorders	**9.6%**	**3.0%**					
Metabolic and nutritional			**8.9%**	**7.7%**	**11.9%**		
decreased appetite	7.8%	1.7%					
Weight loss			1.8%	1.9%	5.1%		
Vascular disorders / Cardiovascular	**3.2%**	**4.7%**	**14.3%**	**13.5%**	**11.9%**		
migraine			8.9%	3.8%	0.0%		
hypertension	1.8%	2.7%	1.8%	1.9%	3.4%		
Ear and labyrinth disorders	**2.8%**	**3.7%**					
vertigo	1.8%	3.3%					
Urogenital			**12.5%**	**13.5%**	**10.2%**		
dysmenorrhea			5.4%	1.9%	1.7%		

For **Study 304** a total of 151 (90.4%) subjects reported TEAEs: 50 (89.3%) in the 25-mg/day group, 47 (90.4%) in the 100-mg/day group, and 54 (91.5%) in the 300-mg/day group. TEAEs related to study drug were higher in the 300mg group 52.5% compared to 44.2% in the 100mg group and 41.1% in the 25mg group.

The following TEAEs were reported most frequently (at least 10% of subjects overall): headache 44.9%, nausea 21.6%, infection 18.0%, dizziness 16.8%, rhinitis 15.0%, asthenia 14.4%, abdominal pain 12.0%, pharyngitis 12.0%, insomnia 11.4%, anorexia 10.2%, diarrhoea 10.2%, and somnolence 10.2%.

For **Study 310** The most commonly experienced TEAEs (incidence of ≥ 4% in any treatment group) were headache (ZNS: 10.3%; CBZ: 12.3%), decreased appetite (ZNS: 7.8%; CBZ: 1.7%), somnolence (ZNS: 6.0%; CBZ: 7.7%), dizziness (ZNS: 3.9%; CBZ: 7.7%), weight decreased (ZNS: 6.8%; CBZ: 0%), fatigue (ZNS: 4.6%; CBZ: 4.0%), rash (ZNS: 2.1%; CBZ: 4.3%), and pyrexia (ZNS: 3.9%; CBZ: 4.0%).

In addition to the most common TEAEs noted above, a notable difference between treatment groups was observed for the Psychiatric disorders SOC (ZNS: 9.3%; CBZ: 4.7%), though the highest incidence of any specific event in this SOC was low (2.1%). In this SOC, the incidence of depression (1.9% overall), depressed mood (0.7% overall), and depressive symptoms (0.2% overall) was low and similar across treatments.

Three TEAEs occurred at an incidence which differed by ≥3% between treatment groups. Weight loss (weight decreased [ZNS, 6.8%; CBZ, 0%]) and decreased appetite (ZNS, 7.8%; CBZ, 1.7%) were reported more often in ZNS-treated subjects, and dizziness (ZNS, 3.9%; CBZ, 7.7%) was reported more often in CBZ-treated subjects.

The most frequent types of TEAEs in each group were consistent with the expected AE profiles of the study medications. Differences between the groups such as higher incidences of decreased appetite, weight loss, and insomnia in the ZNS group, and a higher incidence of dizziness and rash in the CBZ group were also in keeping with the known AE profiles of the two drugs.

Concerning long term safety in the extension study of study 310 (study 355), ZNS and CBZ did not show any new safety or tolerability issues. The incidence of treatment related TEAEs appears to be slightly higher for zonisamide than carbamazepine. The number of serious treatment related TEAEs were low in both groups (5% ZNS and 4% CBZ). No cases of Steven's Johnson syndrome, toxic epidermal necrolysis or metabolic acidosis were identified. The CHMP concluded that no new safety or tolerability issues were identified.

2.5.4. Serious adverse events and deaths

In Study 304 one subject in the 300 mg /day group died in a road traffic accident on day 28 of the study. Limited information was available regarding the event and the investigator reported the event as not related.

Nonfatal serious TEAEs occurred in 9 (5.4%) subjects; all serious TEAEs were unrelated to treatment with study medication.

Other significant adverse events reported included weight loss, rash, maculopapular rash, vesiculobullous rash, kidney calculus, fever, thirst, dehydration, and sweating. Weight loss was reported as an AE by five subjects (3.0% overall), two of whom had weight decreases ≥ 10% or more, one of whom withdrew from the study due to this event.

Adverse events leading to withdrawal were commonest in the 300mg treatment group.

In study 310 Nonfatal SAEs occurred in similar proportions in each treatment group (ZNS: 5.0%; CBZ: 5.7%). One ZNS subject experienced a life-threatening nonfatal SAE (brain neoplasm unrelated to treatment), leading to withdrawal from the study. Ten subjects (three on ZNS, seven on CBZ) experienced nonfatal SAEs which were related to treatment. Both treatment groups had subjects with SAEs requiring or prolonging hospitalization and important medical events.

Individual treatment related SAEs in the ZNS treatment arm concerned purpura (n=1), acute psychosis (n=1) and complex partial seizure (n=1). Treatment related SAEs in the CBZ group concerned suicidal ideation (n=1), rash (n=2), increased hepatic enzyme (n-1), bradycardia (n-1), partial seizures, with sec. generalisation (n=1) and head injury with facial bones fracture (n=1).

One ZNS-treated subject died suddenly during the night. The death was reported at 1 day after receiving the last dose of study drug. The subject was a 50 year old male and had a history of myocardial infarction. ECG at screening was normal. No diagnosis was made and the death was recorded as unexplained and unrelated to treatment.

Rates of discontinuation due to adverse events were similar in both groups. The most commonly reported TEAEs that resulted in discontinuation of therapy were rash (ZNS, 1.1% vs. CBZ, 2.7%), fatigue (ZNS, 1.8 % vs. CBZ, 0%), and dizziness (ZNS, 1.1% vs. CBZ, 1.3%). The remaining TEAEs resulting in discontinuation occurred in < 1.1% of subjects in either group. In addition to these AEs, a slightly higher proportion of ZNS subjects discontinued therapy due to psychiatric disorders (ZNS: 2.5%; CBZ: 1.3%).

2.5.5. Adverse events of interest

Weight loss

A total of 36 ZNS-treated subjects (13.2%) and 4 CBZ-treated subjects (1.4%) had > 10% body weight loss at any post-Baseline visit, but cases of weight loss (weight decreased) were reported as TEAEs in ZNS-treated subjects only (ZNS, 6.8%; CBZ, 0%). This corresponds with an increased incidence of decreased appetite in ZNS-treated subjects (ZNS, 7.8%; CBZ, 1.7%). This event is in accordance with the special warnings and precautions for Zonegran use as it has been commonly reported with adjunctive therapy. Two subjects, both of whom were on ZNS treatment, had > 20% body weight loss. This was not reported as an SAE for either, and both subjects completed the study.

This is a potentially important adverse event affecting over 10% of those treated with Zonisamide, which is of concern.

Metabolic acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with Zonegran treatment. Bicarbonate levels decreased by ≥ 3.5 mmol/L were observed in 121 subjects (51.1%) in the ZNS arm and 45 subjects (17.4%) in the CBZ group. Nine ZNS-treated subjects (3.8%) and 1 CBZ-treated subject (0.4%) had a bicarbonate value of ≤ 16 mmol/L and a decrease from baseline of ≥ 6 mmol/L. There were no corresponding reports of respiratory alkalosis or metabolic acidosis during the study.

Laboratory findings /vital signs

The results from studies 310, 304, and 355 did not provide evidence of an adverse effect of ZNS on haematology and clinical chemistry parameters except for bicarbonate. Isolated abnormal values were observed in some subjects but, given the duration of ZNS treatment in some studies, these findings are consistent with the normal pattern of laboratory values over time.

In study 310, the decreases in bicarbonate (mean −2.8 mmol/L) were generally small to moderate, and were similar to what has been described in previous trials. Decreases from baseline of ≥ 3.5 mmol/L were observed in 121 subjects (51.1%) in the ZNS group and 45 subjects (17.4%) in the CBZ group. Nine ZNS-treated subjects (3.8%) and 1 CBZ-treated subject (0.4%) had a bicarbonate value of ≤ 16 mmol/L and a decrease from Baseline of ≥ 6 mmol/L. Decreased bicarbonate was not reported as an AE in any subject and there were no reports of metabolic acidosis. In study 304 subjects who had a baseline serum bicarbonate level ≥ 17 mEq/L, the incidence of subjects meeting criteria (i.e., postbaseline levels < 17 mEq/L with a corresponding decrease from baseline > 5 mEq/L) at any visit was 3.8% in the 25-mg/d group, 4.2% in the 100-mg/d group, and 15.7% in the 300-mg/d group.

There were no unexpected findings in vital signs, ECGs, physical examinations, or neurological examinations in any of the Phase 3 zonisamide monotherapy studies.

2.5.6. Safety in special populations

Pregnancy

Three subjects became pregnant during Study 310. One subject in the ZNS 400 mg/d group became pregnant during titration. The pregnancy was terminated medically due to "abnormal scan results" which were not further specified. She had no other AEs recorded and was withdrawn from the study. A second subject became pregnant while on CBZ 600 mg. She was discontinued from the study and had a normal vaginal delivery at 39 weeks; no other events were reported. The third subject on CBZ 600 mg became pregnant and was withdrawn from the study. After her last menstrual period, study drug was discontinued. The outcome of the pregnancy is unknown.

In Study 304, two subjects became pregnant and were withdrawn from the study. One subject had an elective abortion; the other had a normal pregnancy and delivered a healthy baby boy without any complications.

There were no reported pregnancies during Study 355.

2.5.7. Discussion on clinical safety

The most frequent types of TEAEs in each treatment group were consistent with the expected safety profiles of the study medications.

Differences between the groups such as higher incidences of decreased appetite, weight loss, and insomnia in the ZNS group and a higher incidence of dizziness and rash in the CBZ group were also in accordance with the specific and established safety profiles of each of the two drugs.

2.6. Risk management plan

Version 7 of the RMP is the current one at the time of approval of this variation. The reasons for the updates submitted since the start of this variation procedure (version 5 of the RMP) were to reflect the availability of the monotherapy study data and in order to convert to the EMA template format. The changes to the RMP are extensive due to reformatting; however, the content was consistent with the previously submitted versions of the safety specification (version 3) and pharmacovigilance plan (version 4).

No new risks have been added to the RMP as a result of completion of the monotherapy studies or as a consequence of PSUR 8 and thus no additional risk minimisation measures are planned.

The MAH was requested in the first RSI to amend the following areas of the RMP:

- Renal effects seen in the non-clinical studies in section 1.1.1 of the safety specification.
- The risk of osteopenia is linked to the risk of metabolic acidosis and should be mentioned throughout the RMP.
- The RMP was updated to reflect the agreed wording of the SmPC in relation to currently ongoing or recently completed procedures throughout the RMP;

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.7. Changes to the Product Information

Apart from the addition of a table in section 5.1 and the change to the instructions on the disposal of the product in 6.6, the CHMP agreed with the changes proposed by the MAH as follows:

ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

o monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see 5.1);

4.2 Posology and method of administration

Posology - Adults

Dosage escalation and maintenance

Zonegran may be taken as monotherapy or added to existing therapy in adults. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 1. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Withdrawal

When Zonegran treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of adult patients, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses (where necessary).

Table 1. Adults – recommended dosage escalation and maintenance regimen

Treatment Regimen	**Titration Phase**			**Usual Maintenance Dose**
Monotherapy - Newly diagnosed adult patients	**Week 1 + 2**	**Week 3 + 4**	**Week 5 + 6**	300 mg per day (once a day). If a higher dose is required: increase at two-weekly intervals in increments of 100 mg up to a maximum of 500 mg.
	100 mg/day (once a day)	200 mg /day (once a day)	300 mg / day (once a day)	
Adjunctive therapy - with CYP3A4-inducing agents (see section 4.5)	**Week 1**	**Week 2**	**Week 3 to 5**	300 to 500 mg per day (once a day or two divided doses).
	50 mg/day (in two divided doses)	100 mg /day (in two divided doses)	Increase at weekly intervals in increments of 100 mg	
- without CYP3A4-inducing agents; or with renal or hepatic impairment	**Week 1 + 2**	**Week 3 + 4**	**Week 5 to 10**	300 to 500 mg per day (once a day or two divided doses). Some patients may respond to lower doses.
	50 mg/day (in two divided doses)	100 mg / day (in two divided doses)	Increase at two-weekly intervals in increments of up to 100 mg	

General dosing recommendations for Zonegran in special patient populations

Zonegran hard capsules are for oral use….

4.8 Undesirable effects

[…]

The most common adverse reactions in controlled adjunctive-therapy studies in adults were somnolence, dizziness and anorexia. The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. The incidence of markedly abnormally low serum bicarbonate (a decrease to less than 17 mEq/l and by more than 5 mEq/l) was 3.8%. The incidence of marked decreases in weight of 20% or more was 0.7%.

Adverse reactions associated with Zonegran obtained from clinical studies and post-marketing surveillance are tabulated below. The frequencies are arranged according to the following scheme:

very common	≥ 1/10
common	≥ 1/100 to < 1/10
uncommon	≥ 1/1,000 to < 1/100
rare	≥ 1/10,000 to < 1/1,000
very rare	< 1/10,000
not known	cannot be estimated from the available data

[…]

Table 2 Adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release

System Organ Class (MedDRA terminology†)	**Very Common**	**Common**	**Uncommon**
Infections and infestation			Urinary tract infection Pneumonia
Blood and lymphatic disorders			Leukopenia Thrombocytopenia
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric Disorders		Agitation Depression Insomnia Mood swings Anxiety	Confusional state Acute psychosis Aggression Suicidal ideation Hallucination
Nervous system disorders		Ataxia Dizziness Memory impairment Somnolence Bradyphrenia Disturbance in attention Paraesthesia	Nystagmus Speech disorder Tremor Convulsion
Eye disorders		Diplopia	
Respiratory, thoracic and mediastinal disorders			Respiratory disorder
Gastrointestinal disorders		Constipation Diarrhoea Dyspepsia Nausea Vomiting	Abdominal pain
Hepatobiliary disorders			Cholecystitis acute
Skin and subcutaneous tissue disorders		Rash	Pruritus Ecchymosis
General disorders and administration site conditions		Fatigue Pyrexia Irritability	
Investigations	Decreased bicarbonate	Weight decreased Blood creatinine phosphokinase increased Alanine aminotransferase increased Aspartate aminotransferase increased	Urine analysis abnormal

† MedDRA version 13.1

5.1 Pharmacodynamic properties

[…]
Clinical efficacy

Monotherapy in partial seizures with or without secondary generalisation.

Efficacy of zonisamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures. Subjects

were randomised to carbamazepine and zonisamide received treatment for a duration of up to 24 months depending on response. Subjects were titrated to the initial target dose of 600 mg carbamazepine or 300 mg of zonisamide. Subjects who experienced a seizure were titrated to the next target dose i.e. 800 mg carbamazepine or 400 mg of zonisamide. Subjects who experienced a further seizure were titrated to the maximal target dose of 1200 mg carbamazepine or 500 mg zonisamide. Subjects who were seizure-free for 26 weeks at a target dose level continued on this dose for another 26 weeks. Main outcomes of this study are presented in this table:

	Zonisamide	**Carbamazepine**	N	
n (ITT population)	281	300		
Six months seizure freedom			Diff	$CI_{95\%}$
PP-population*	79.4%	83.7%	-4.5%	-12.2% ; 3.1%
ITT-population	69.4%	74.7%	-6.1%	-13.6% ; 1.4%
< 4 seizures during 3 month baseline period	71.7%	75.7%	-4.0%	-11.7% ; 3.7%
> 4 seizures during 3 month baseline period	52.9%	68.9%	-15.9%	-37.5% ; 5.6%
Twelve months seizure freedom				
PP-population	67.6%	74.7%	-7.9%	- 17.2% ; 1.5%
ITT-population	55.9%	62.3%	-7.7%	- 16.1% ; 0.7%
< 4 seizures during 3 month baseline period	57.4%	64.7%	-7.2%	-15.7% ; 1.3%
> 4 seizures during 3 month baseline period	44.1%	48.9%	-4.8%	-26.9% ; 17.4%
Seizure Sub-type (6 month seizure freedom-PP population)				
All partial	76.4%	86.0%	-9.6%	-19.2% ; 0.0%
Simple partial	72.3%	75.0%	-2.7%	-20.0% ; 14.7%
Complex partial	76.9%	93.0%	-16.1%	-26.3% ; -5.9%
All generalized Tonic-Clonic	78.9%	81.6%	-2.8	-11.5% ; 6.0%
Secondary Tonic-Clonic	77.4%	80.0%	-2.6%	-12.4% ; 7.1%
Generalized Tonic-Clonic	85.7%	92.0%	-6.3%	-23.1% ; 10.5%

PP = Per Protocol Population; ITT = Intent To Treat Population
**Primary endpoint*

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults

In adults,……

6.6 Special precautions for disposal

Any unused medicinal product or waste marterial should be disposed in accordance with local requirements

ANNEX IIIB PACKAGE LEAFLET

WHAT ZONEGRAN IS AND WHAT IT IS USED FOR

[…]

Zonegran is used to treat ~~adults who are already taking other antiepileptic medicines but are still experiencing~~ seizures that affect one part of the brain (partial seizure), which may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zonegran may be used:
- On its own to treat seizures in adults.
- With other antiepileptic medicines to treat seizures in adults.

HOW TO TAKE ZONEGRAN

[…]

The usual adult dose

When you take Zonegran on its own:
- The starting dose is 100 mg taken once a day.
- This may be increased by up to 100 mg at intervals of two weeks.
- The usual dose is 300 mg once a day.

When you take Zonegran with other antiepileptic medicines:
- The starting dose is 50 mg daily taken in two equal doses of 25 mg.
- […]

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

Zonisamide is a known anti-epileptic agent indicated for the adjunctive treatment of adult patients with partial seizures, with or without secondary generalisation. As such, the antiepileptic properties of zonisamide are not at stake.

In order to support a monotherapy indication it is necessary to establish the correct dose for the monotherapy indication, and to demonstrate the efficacy and safety of zonisamide in the absence of anti-epileptic co-medication.

Study 310 showed that zonisamide has similar response rates in the control of partial seizures to carbamazepine retard. The study was performed in accordance with EMA guidance on the investigation of medicinal products in the treatment of epileptic disorders and the scientific advice given. The step wise fixed dose increments based on response and the long follow up period recommended in the guideline is meant as a check on assay sensitivity.

The proportion of subjects exposed to zonisamide in the per protocol population (primary analysis) who were seizure free for 6 months was 79.4% compared to 83.7% in those exposed to carbamazepine, a difference of -4.5% in favour of carbamazepine (95% confidence interval (-12.2%, 3.1%).

Additional evidence for efficacy comes from the fixed dose response study, study 304. Although the results of study 304 are inconclusive, i.e. not statistically significant, the trend in favour of the 300 mg dose is considered supportive for the monotherapy claim.

Zonisamide could offer an alternative in the therapeutic armamentarium because of its different mechanism of action, the once daily dosing, and a different interaction profile.

Uncertainty in the knowledge about the beneficial effects

The results of Study 310, which was carried out in line with EMA guidance and the scientific advice, showed that in the per protocol population 79.4% of those exposed to zonisamide were seizure free at 6 months compared to 83.7% of those exposed to carbamazepine. This was an actual difference of -4.5% in favour of carbamazepine (CI -12.2%, 3.1%). The lower confidence interval of 12.2 was slightly outside the pre-defined absolute inferiority margin of 12%. Initially, the assay sensitivity of the trial was questioned, but this has been resolved during subsequent discussion (see discussion on clinical efficacy).

Zonisamide showed consistently lower results than carbamazepine in study 310. However, overall the response rates were high in both study arms (80%), and the difference in point estimates was less than 5%. Retention rates were similar, which was reassuring.

Risks

Unfavourable effects

With respect to safety there were no large differences between zonisamide and carbamazepine in incidence of adverse events, or incidence of severe or serious adverse events. The adverse event profile of each compound was consistent with each established safety profiles. It cannot be concluded, based on the observed adverse events, that one drug is superior to the other in terms of safety: their safety profiles are different. ZNS has a better profile regarding skin events whereas CBZ has a better one with respect to psychiatric disorders. The choice of the most appropriate treatment would depend on the patient’s history and circumstances, and the patient’s specific vulnerability to these events.

Uncertainty in the knowledge about the unfavourable effects

No unexpected unfavorable effects have emerged. Given the small numbers, low incidences and small sample size, the differences evidenced in the studies presented in this submission are not considered of clinical significance.

Balance

Importance of favourable and unfavourable effects

While Zonisamide has shown a consistently lower response rate as compared to CBZ, in the primary - and most important- analysis ZNS still showed a high response rate. Additionally, the difference in point estimates between ZNS and CBZ was less than 5%, and retention rates were similar in the two arms.

In light of the fact that the safety profile differs qualitatively and that there were no large safety differences between zonisamide and carbamazepine in incidence of adverse events, or incidence of severe or serious adverse events, the CHMP considered that it could offer an alternative to CBZ treatment because of the different mechanism of action, once daily dosing, and the interaction profile.

The choice of appropriate treatment would depend on the patient's history, circumstances, and vulnerability to the ADR profile of the medication of choice.

Benefit-risk balance

The anti-epileptic properties of Zonisamide as such are not at stake, as efficacy in the add-on setting has been proven, and the adverse event profile of each compound was consistent with the expected adverse reaction profiles.

Zonisamide could offer an alternative in the therapeutic armamentarium because of the different mechanism of action, once daily dosing, and the interaction profile.

Divergent positions are presented in Appendix 1.

Discussion on the benefit-risk assessment

In order to support a monotherapy indication it is necessary to establish the correct dose for the monotherapy indication and to demonstrate the efficacy and safety of Zonisamide in the absence of other anti-epileptic co-medication.

The pre-defined inferiority margin of 12% was not met, with a lower 95% CI for the inferiority margin of -12.2%: the MAH substantiated the assay sensitivity and this allowed the conclusion that a lower level of efficacy was acceptable because of the high response rate shown to ZNS treatment, the less than 5% difference between point estimates (absolute and relative) and the similar retention rates of ZNS and CBZ in the pivotal clinical trial.

The different safety profile of ZNS versus CBZ can offer an alternative treatment that can be more appropriate depending on the patient's specific vulnerability to adverse reactions. In addition the once daily dose of ZNS offers an advantage in terms of convenience and presumably also for compliance. The choice of treatment will depend, in clinical practice, on the patient's medical history.

Therefore, the CHMP considered that the benefit risk balance for zonisamide in the new indication "monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy" is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include monotherapy. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPCwere updated. The Package Leaflet is updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template version 7.3.1.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, Annex II and Package Leaflet.

Divergent positions are presented in Appendix 1.

Conditions and requirements of the marketing authorisation

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of the approved indication of adjunctive treatment of partial seizures with or without secondary generalisation in adults to include monotherapy in adults with newly diagnosed epilepsy.

Summary

Please refer to the CHMP AR report for this extension variation.

Appendix 1

Divergent Position

The undersigned member of CHMP did not agree with the CHMP's opinion recommending the adoption of the variation to the terms of the Marketing Authorisation, concerning the new therapeutic indication for Zonegran.

The reasons for the divergent opinion were as follows:

The benefit-risk balance of zonisamide in monotherapy is considered unfavourable. In particular, the clinical benefit associated with the observed results for Zonegran is questionable, as the assay sensitivity has not been adequately substantiated, and the high response rate in the pivotal trial warranted a more precise estimate in comparison to carbamazepine to adequately establish and contextualise the efficacy of zonisamide.

London, 24 May 2012

Kristina Dunder