EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/304195/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zebinix

International non-proprietary name: eslicarbazepine acetate

Procedure No. EMEA/H/C/000988/II/0053

Note

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

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Anti-epileptic Drug
ALT	alanine aminotransferase
ARD	Average Risk Difference
AST	aminotransferase
AUC	Area under the plasma concentration-time curve
BID	twice daily
BL-VAS	Bond-Lader visual analogue scales
BMI	Body Mass Index
CBZ	Carbamazepine
CBZ-CR	Carbamazepine controlled release
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalogram
ERA	Environmental Risk Assessment
ESL	Eslicarbazepine acetate
FAS	Full Analysis Set
Fpen	Market penetration factor
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HPLC	High performance liquid chromatography
ILAE	International Leagues Against Epilepsy
ITT	Intent-to-Treat
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass spectrometry
NI	Non-inferiority
NOAEL	No Observed Adverse Effect Level
PEC	Predicted environmental concentration
PK	Pharmacokinetics
PNEC	Predicted No-Effect Concentration
PP	Per protocol
POS	Partial-onset seizures
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
RRD	Relative Risk Difference
SAE	Serious Adverse Events
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA queries
SPP	Per Protocol Subset
SUDEP	Sudden unexplained death in epilepsy

SOC	System organ classes
TEAE	Treatment-emergent adverse events
QD	Quaque Die, once daily
QOL	Quality of life
QOLIE-31	Quality of Life in Epilepsy Inventory-31
QRD	Quality Review of Documents
ULN	upper limit of normal
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bial - Portela & Cª, S.A. submitted to the European Medicines Agency on 5 April 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication for the tablet formulation to include the use of Zebinix as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy, in addition to the previously authorised indication as adjunctive therapy. As a consequence, Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. This submission includes an updated RMP (version 15.0). In addition, the MAH is claiming an additional 1-year period of market protection under Article 14(11) of Regulation (EC) No 726/2004.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0015/2015 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0015/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The MAH withdrew the request during the procedure.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Ondřej Slanař

Timetable	Actual dates
Submission date	5 April 2016
Start of procedure:	23 April 2016
CHMP Rapporteur Assessment Report	17 June 2016
CHMP Co-Rapporteur Assessment Report	17 June 2016
PRAC Rapporteur Assessment Report	22 June 2016
PRAC members comments	29 June 2016
PRAC Outcome	7 July 2016
CHMP members comments	11 July 2016
Updated CHMP Rapporteurs Joint Assessment Report	15 July 2016
Request for supplementary information	21 July 2016
Submission	14 October 2016
Re-start	17 October 2016
CHMP Rapporteur Assessment Report	15 November 2016
PRAC Rapporteur Assessment Report	18 November 2016
PRAC members comments	23 November 2016
Updated PRAC Rapporteur Assessment Report	24 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	5 December 2016
CHMP members comments	5 December 2016
Updated CHMP Rapporteur Assessment Report	8 December 2016
Request for Supplementary Information (2nd)	15 December 2016
Submission	19 January 2017
Re-start	23 January 2017
CHMP Rapporteur Assessment Report	22 February 2017
PRAC Rapporteur Assessment Report	2 March 2017
PRAC members comments	6 March 2017
Updated PRAC Rapporteur Assessment Report	6 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Rapporteur Assessment Report	16 March 2017
Opinion	23 March 2017

2. Scientific discussion

2.1. Introduction

Epilepsy is a heterogeneous and serious brain disorder characterised by the occurrence of recurrent or a high risk of recurrent unprovoked, spontaneous seizures. Amongst the estimated 50 million people worldwide affected by epilepsy, more than 50% have partial-onset seizures (POS). POS are initially confined to a discrete area of the cerebral cortex, but may spread to involve both cerebral hemispheres resulting in a secondary generalisation. POS can manifest as motor, sensory, automatic or psychic symptoms and, in case of secondary generalisation, as absences, tonic, clonic, tonic-clonic, myoclonic or tonic seizures.

Based on the 1981 Classification by the International League Against Epilepsy (ILAE), which is still widely used, POS can be divided in 3 different seizure subtypes, including Type IA (simple partial seizures) and IB (complex partial seizures), depending on whether consciousness is affected, as well as IC (with secondary generalised tonic-clonic convulsions). In a more recent revised operational classification by ILAE (2017), the term focal seizures is preferred over POS and focal seizures, which may or may not evolve to generalised tonic-clonic seizures, are further characterised by awareness versus impaired awareness and motor versus non-motor onset.

According to relevant treatment guidelines (e.g. ILAE, United Kingdom National Institute for Health and Care Excellence, etc) first line treatment of patients with newly diagnosed POS consists of monotherapy with an anti-epileptic drug (AED). Approximately 60% of epilepsy patients manage to attain long-term seizure freedom on a single AED (Stephen, 2012) and this is the primary treatment objective. The remaining patients require adjunctive treatment, which is usually applied after two failed monotherapies.

Traditionally, AEDs are first studied in add-on trials in refractory epilepsy patients. As a result, clinical testing and approval for monotherapies in newly diagnosed patients often occurs years after development in the adjuvant setting. Monotherapy of epilepsy can give certain advantages for patients when compared with adjunctive therapy including improved patient compliance as well as a decreased risk for drug interactions and better tolerability. There remains a therapeutic need for additional monotherapy options.

Eslicarbazepine acetate (BIA 2-093, ESL) acts as a voltage-gated sodium channel blocker which competitively interacts with site 2 of the inactivated state of the channel. It is a third-generation, single-enantiomer member of the long-established family of first-line dibenz/b,f/azepine AEDs represented by carbamazepine (CBZ) and oxcarbazepine.

ESL is the active substance of Zebinix which was approved in the European Union/European Economic Area through the Centralised Procedure by Commission Decision in 2009 as adjunctive therapy in adults with POS with or without secondary generalisation. The indication was later extended for adjunctive therapy of POS in children aged more than 6 years. Zebinix is available as immediate release tablets containing 200 mg, 400 mg, 600 mg and 800 mg of ESL and as an oral suspension (50 mg/ml). The recommended starting dose in adults for add-on therapy is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be further increased to 1,200 mg once daily. Children weighing less than 60 kg are dosed based on their weight.

In the present application, the MAH proposed to extend the indication to monotherapy of adult with POS with or without secondary generalisation at doses up to 1600 mg/day. To support the application, the MAH submitted the results of a Phase 3 clinical trial (BIA-2093-311, henceforth referred to as study 311). Furthermore, supportive safety data were provided from 2 identically designed conversion-to-monotherapy studies (studies 093-045 and 093-046, henceforth referred to as studies 045 and 046).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. An updated environmental risk assessment (ERA) has been provided.

2.2.1. Ecotoxicity / environmental risk assessment

An updated ERA was provided taking into account the proposed new extended target population. The same EPAR has previously been reviewed and was accepted in procedure EMEA/H/C/000988/X/0050/G. A refined market penetration factor (Fpen) of 0.001 was calculated for the purpose of the Phase II Tier A assessment based on the prevalence of POS in both adults and paediatric patients using epidemiological data by Forsgren et al. (2005) and Giussani et al. (2014) as well as sales forecast data in the five largest EU countries resulting in a market share of 27.27%. Based on the new proposed maximum maintenance dose of ESL 1600 mg/day in POS monotherapy, the predicted environmental concentration in surface water (PEC_{sw}) was refined at 0.688 µg/L. Using an assessment factor of 100, and a Predicted No-Effect Concentration for the sediment compartment ($PNEC_{sediment}$) of 1µg/L (Goodband and Mullee, 2011), the resulting risk quotient was 0.688, which is below the trigger value of 1.

Based on the updated ERA, ESL is not expected to pose a risk to the environment, when used according to the approved indication and posology.

2.2.2. Discussion on the non-clinical aspects

As previously shown during the initial marketing authorisation application of Zebinix as adjunctive therapy of POS in adult patients, ESL is rapidly hydrolysed in humans thus not yielding measurable plasma concentrations while there is a measurable exposure in animal studies. Exposure to eslicarbazepine, the main active metabolite of ESL, at the identified No Observed Adverse Effect Levels (NOAELs) in all animal species tested, were below those achieved in man. In man, the area under the plasma concentration-time curve (AUC) value for eslicarbazepine at a dose of 800 mg per day was 268.38 µg.h/mL (males) as compared to 136.13/104.74, 0.98/3.36 and 29.99/33.12 µg.h/mL (male/female animals) at the NOAELs of 150, 20 and 40 mg/kg/day in mice, rats and dogs, respectively. Hence, no safety margins towards human exposure could be calculated.

This finding was considered to be equally applicable for the present application including the new proposed maximum dose for monotherapy (ESL 1600 mg/day). Therefore, the CHMP agreed that no new non-clinical data were needed in support of this application.

With regards to ERA, based on the updated data, Zebinix is not expected to pose a risk to the environment when used according to the SmPC.

2.2.3. Conclusion on the non-clinical aspects

The CHMP concluded that no new non-clinical data were needed in order to support the present application. With regards to the updated ERA, ESL is not expected to pose a risk to the environment. Altogether, the application was considered acceptable from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The MAH confirmed that the clinical trials were performed in accordance with GCP.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 - Tabular overview of clinical studies

Study	No. of subjects randomised (Age range)	Study design	Treatment regimen
Pivotal study in epileptic adults			
BIA-2093-311	815 (≥18 years)	Multinational, randomised, DB, active-controlled, parallel-group, multiple-dose study: • 7-day Screening Period • 1-week Titration Period • 1-week Stabilisation Period • 26-week Evaluation Period during which the dosage was up-titrated if a subject experienced a seizure • 26-week Maintenance Period • Extension Phase until database lock • Tapering-off Period (1-week steps of down-titration and 4-week follow-up) OR continue to OL treatment	ESL or CBZ (randomised in a 1:1 ratio) Dose level A: • ESL: 400 mg QD up-titrated to 800 mg QD • CBZ-CR: 200 mg QD up-titrated to 200 mg BID Dose level B: • ESL: 1200 mg QD • CBZ-CR: 300 mg BID up-titrated to 400 mg BID Dose level C: • ESL: 1600 mg QD • CBZ-CR: 500 mg BID up-titrated to 600 mg BID
Supportive studies in epileptic adults: US supportive study pool			
093-045 and -046	365 (16–70 years)	Multicentre, randomised, double-blind and historical-controlled studies: • 2-week titration • 6-week AED taper conversion • 10-week treatment period	ESL 1600 mg or 1200 mg QD (randomised in a 2:1 ratio)

AED = anti-epileptic Drug; BID = twice daily; CBZ-CR = carbamazepine controlled-release; DB = double-blind; ESL = eslicarbazepine acetate; OL = open-label; QD = once daily

2.3.2. Pharmacokinetics

Sparse pharmacokinetic (PK) sampling has been performed in pivotal monotherapy study 311. Blood samples (10 mL) for measurement of eslicarbazepine (BIA 2-194), the main active metabolite of ESL, and the CBZ levels were drawn at Visit 2 (A2/B2/C2), Visit 4 (A4/B4/C4) and Last Extension Phase Visit (day of stop of treatment). See section 2.4.2. for an overview of the study design.

The levels of CBZ in human plasma study samples from study 311 were determined by validated high performance liquid chromatography (HPLC) method with mass MS/MS detection. The method was found suitable for the determination of CBZ in human plasma in the range from 20.0 to 20000 ng/mL. The levels of BIA 2-194 (eslicarbazepine) in human plasma study samples were determined by validated chiral HPLC method with triple-stage quadrupole MS/MS detection. The method was found suitable for the determination of BIA 2-194 in human plasma in the range from 50.0 to 25000 ng/mL.

The results of the analysis of exposure to eslicarbazepine and CBZ by visit and dose level are presented in

Figure 1and Figure 2.

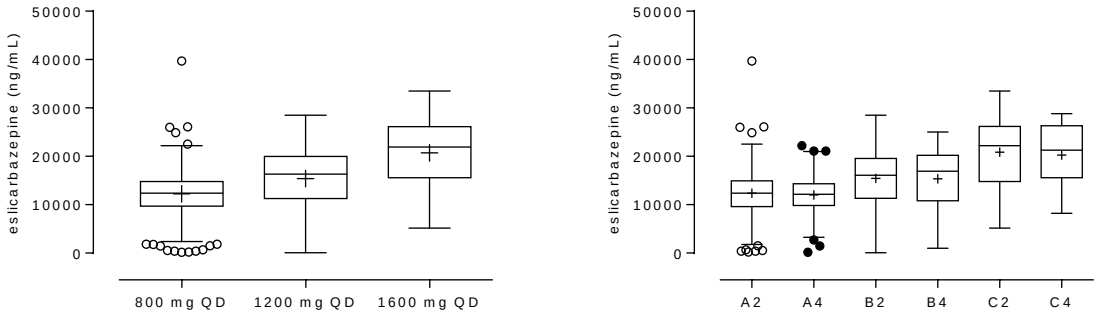


Figure 1 - Eslicarbazepine plasma levels by visit and correspondent dose levels in Study 311

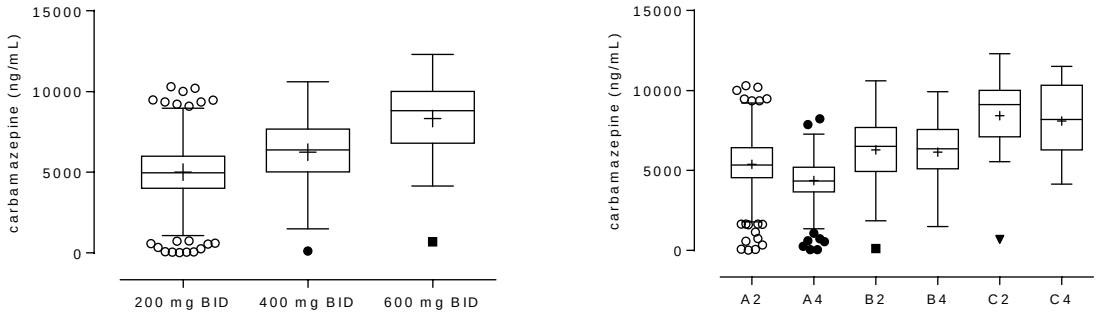


Figure 2 – CBZ plasma levels by visit and correspondent dose levels in Study 311

Plasma exposure to eslicarbazepine increased in dose-dependent manner [median plasma levels were 12400 ng/mL, 16300 ng/mL, and 21900 ng/mL for ESL QD doses of 800 mg, 1200 mg, and 1600 mg QD, respectively]. Likewise, plasma exposure to carbamazepine increased in a dose-dependent manner [median plasma levels were 4970 ng/mL, 6380 ng/mL, and 8810 ng/mL for CBZ BID doses of 200 mg, 400 mg, and 800 mg, respectively].

2.3.3. Discussion on clinical pharmacology

Overall, the bioanalytical methods of CBZ and eslicarbazepine determination in human plasma were considered to have been successfully validated. Validation was generally performed in accordance with the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2).

Sparse plasma sampling was performed in study 311. The data, although sparse, confirmed dose proportionality of eslicarbazepine exposure, and also show mild increase in plasma concentrations over the time period between visits. While a direct comparison between mono- and add-on therapy is biased due to the presence of other concomitant AEDs in the add-on therapy setting and since for data from sparse sampling, some variability can be anticipated, the exposure in study 311 was similar to that previously reported in the add-on setting by means of simulated data from a population PK model (median eslicarbazepine plasma concentrations at steady state were ~10500 ng/mL for 800 mg, and ~15700 ng/mL for 1200 mg ESL). Exposure data for CBZ have also been presented, and seem to be in accordance with known PK properties of this active substance.

2.3.4. Conclusions on clinical pharmacology

The CHMP concluded that the application was acceptable with regards to clinical pharmacology.

2.4. Clinical efficacy

To support this application, one pivotal phase 3 trial (study 311) was conducted to investigate the effect of ESL as monotherapy in patients with newly diagnosed POS. In addition, supportive data from two identically designed conversion-to-monotherapy studies (study 045 and 046) were provided.

2.4.1. Dose response studies

No dose-response studies have been conducted within the POS monotherapy clinical development program.

The dose range (ESL 800, 1200 and 1600 mg/day) investigated in the pivotal study 311 was selected on the basis of results from previous clinical studies, including Phase 3 studies in adults with partial-onset epilepsy in which ESL was used as add-on therapy. The results of these studies supported the use of ESL 800 and 1200 mg once daily (QD). A dose of 400 mg was also investigated in 2 of the 3 Phase 3 studies but was not found to be effective. Consequently, ESL 800 mg QD was chosen as the lowest dose for study 311. ESL 1600 mg was chosen by the MAH as the highest dose level in study 311 taking into account the tolerability profile in studies for other indications, namely bipolar disorder and neuropathic pain (studies BIA-2093-206, -207, 307 and 308). According to the MAH no particular safety concerns were found for this dose. Reference is furthermore made to safety data for ESL doses up to 2400 mg in healthy subjects and for ESL monotherapy in subjects with bipolar disorder, as well as published results of clinical studies with oxcarbazepine, a drug similar to ESL, in which better tolerability of higher doses in monotherapy as compared to adjunctive therapy was found.

2.4.2. Main study

Study BIA-2093-311: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomised, active-controlled, parallel-group, multicentre clinical study

2.4.2.1. Methods

This was a phase 3, multinational, randomised, double-blind, parallel-group, active-controlled non-inferiority study conducted in adults (≥ 18 years) with newly diagnosed epilepsy experiencing POS.

The study consisted of the following study phases:

- Screening period (1 week)
- Titration period (1 week)
- Stabilisation period (1 week)
- Evaluation period (26 weeks)
- Maintenance period (26 weeks)
- Extension phase (blinded; including down-titration and follow-up, unless the subject continued with open-label treatment in the open-label extension study).

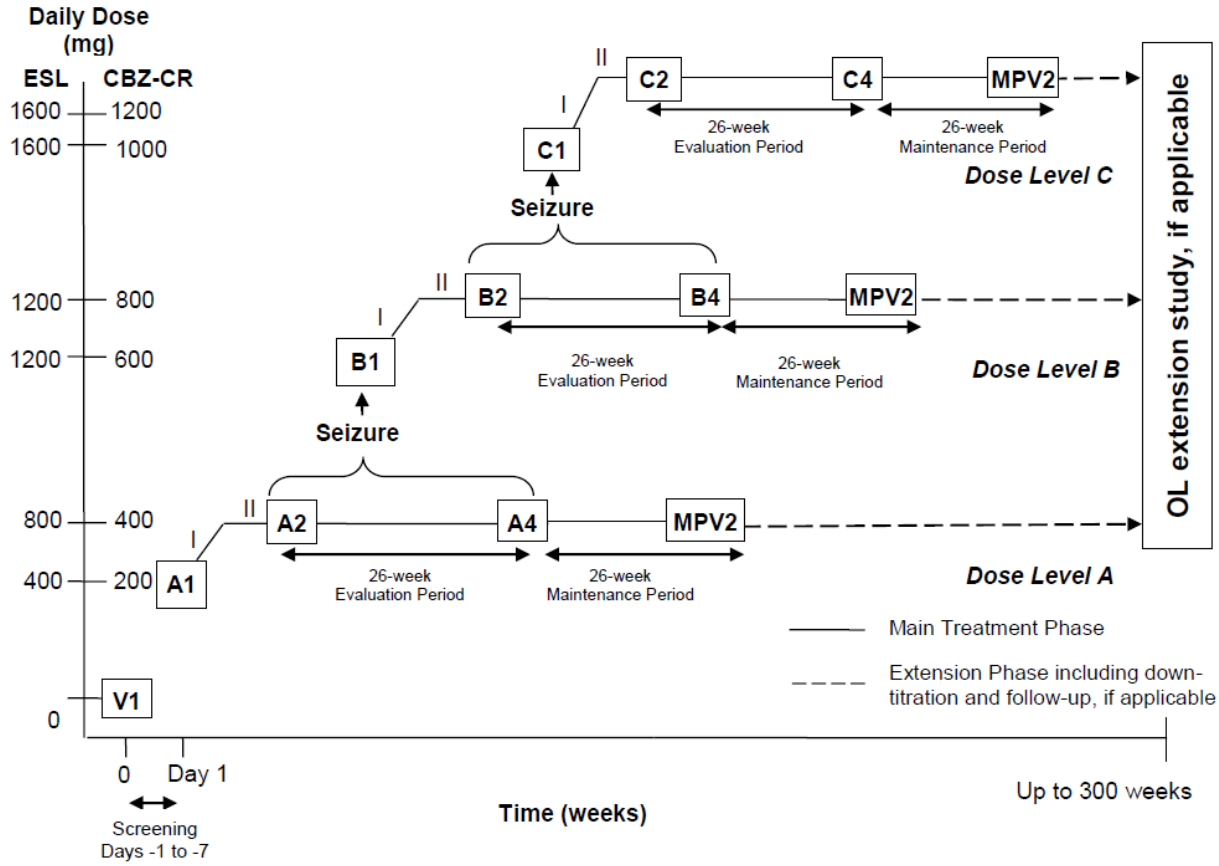


Figure 3 – Design of Study 311

A1, B1, C1 = start of the 1-week Titration Period; A2-A4, B2-B4, C2-C4 = visits of the 26-week Evaluation Period; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; I = 1-week Titration Period; II = 1-week Stabilisation Period; MPV2 = last visit of the 26-week Maintenance Period; OL = open-label; V1 = Screening Visit.

The study was designed with stepwise fixed dose increments based on individual response with 3 dose levels:

- level A: ESL 800 mg QD, CBZ-CR 200 mg BID (400 mg/day),
- level B: ESL 1200 mg QD or CBZ-CR 400 mg BID (800 mg/day), and
- level C: ESL 1600 mg QD or CBZ-CR 600 mg BID (1200 mg/day).

During the titration period, subjects received either ESL 400 mg QD or CBZ-CR 200 mg QD before increasing to the first target dose (dose level A: ESL 800 mg QD, CBZ-CR 200 mg BID). This was followed by a 1-week Stabilisation Period and a 26-week Evaluation Period.

If a seizure occurred (after the respective titration and stabilisation period) during the Evaluation period at dose level A or B, respectively, subjects had their dose increased over a further titration period to the next higher dose level as soon as possible (within 7 days after the seizure), followed by a further stabilisation period. A seizure during titration or stabilisation period did not lead to changes in the scheduled doses.

If a seizure occurred during the Evaluation period at the highest dose level (C), at any dose during the Maintenance Period or during the Extension Phase subjects were withdrawn from the study.

Subjects who remained seizure-free for 26 weeks at any dose in the Evaluation Period continued to receive the allocated treatment under double-blind conditions during the 26-week Maintenance Period and subsequent Extension Phase until the database was locked. As soon as the end of the double-blind study was

announced (when all recruited subjects who had not discontinued early, had attended either Visit A4, B4 or C4 and had been treated with double-blind investigational medicinal product for at least 54 weeks), subjects could be moved forward directly into the Extension phase, i.e. for these subjects the maintenance period was to be terminated early or skipped altogether.

Subjects who benefit from treatment at the end of double-blind study were given the option to enrol in an extension study. This study was ongoing at the time of this application and no results had been provided.

Study duration up to the end of the Main Treatment Phase: Minimum of 55 weeks (i.e. 54 weeks of treatment; for subjects who did not experience a seizure during evaluation/main period) to a maximum of 111 weeks due to the escalation in dose if a seizure occurred.

Study participants

Key inclusion criteria were defined as follows:

- Males or female subjects ≥18 years of age.
- Newly diagnosed epilepsy with at least 2 well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalisation) with clear focal origin, documented clinically OR by electroencephalogram (EEG) OR imaging studies, within 12 months of Visit 1. In this context, seizures that occurred within a period of 48 hours were counted as 1 seizure.
- At least 1 seizure during the previous 3 months.

Key exclusion criteria were defined as follows:

- History of pseudo-seizures, seizures occurring only in clusters, absence, myoclonic, clonic, tonic or atonic seizures.
- Documented EEG findings within 12 months of Visit 1 suggestive of primarily generalised epilepsy.
- History of status epilepticus within the 3 months prior to Visit 1.
- Known progressive neurologic disorder (progressive brain disease, epilepsy secondary to progressive cerebral lesion) as assessed by magnetic resonance imaging or computer tomography.
- Former or current use of any AED, except for the use of a single AED for a maximum duration of 2 weeks before Visit 1.
- Previous regular use of ESL or CBZ (previous use as acute treatment for seizures in an emergency situation was not an exclusion criterion).
- Use of mono-amine oxidase inhibitors, tricyclic antidepressants, nefazodone, isoniazid, or protease inhibitors or any other anti-retroviral agents (e.g. efavirez) that may have raised the levels of CBZ-CR.
- History of uncontrolled psychiatric illness or mood disorder requiring electro-convulsive or drug therapy within the previous 6 months, a history of suicide attempt, schizophrenia, chronic treatment with benzodiazepines (except short-acting benzodiazepines) or barbiturates.
- Judged clinically to have a suicidal risk in the opinion of the investigator based upon a clinical interview and the Columbia Suicide-Severity Rating Scale.
- Uncontrolled cardiac (including atrioventricular block and other clinically significant electrocardiographic abnormalities), renal, hepatic, endocrine, gastrointestinal, metabolic, haematological or oncology disorder.
- History of bone marrow depression.

- History of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
- Relevant clinical laboratory abnormalities (e.g. sodium <130 mmol/L, alanine or aspartate transaminases >2 × the upper limit of normal, white blood cell count <3000 cells/mm3) (measured at Visit 1).
- Estimated glomerular filtration rate <60 mL/min/1.73 m2 (measured at Visit 1).
- Subjects of Asian ancestry who tested positive for the presence of the human leucocyte antigen B*1502 allele.

Treatments

Patients in study 311 received one of the following treatments

- Research therapy:
  - ESL tablets, containing 400 or 800 mg ESL, commercial formulation.
  - Placebo tablets as appropriate.
- Reference therapy:
  - Tegretol-CR tablets, containing 200 or 400 mg CBZ.
  - Carbatrol-XR (extended release) tablets, containing 100 mg CBZ during titration period(s), as Tegretol-CR has no 100 mg formulation.
  - Placebo tablets as appropriate.

Treatment was taken orally in the morning and in the evening, irrespective of meals, separated by approximately 12 hours.

The 3 dose levels of ESL in study 311 were 800 mg/day, 1200 mg/day and 1600 mg/day.

The 3 respective dose levels of the active comparator CBZ-CR were 400mg, 800 mg and 1200 mg/day.

Dose reductions in case of tolerability issues were not allowed, except in the context of down-titration in order to stop treatment.

Concomitant AED:

Any AED was prohibited during the study, however, AEDs as rescue treatment for a seizure as well as up-dosing of a new AED within 7 days before the start of down-titration in the framework of early discontinuation or study completion (except ESL subjects continuing in the open-label extension part) were allowed and not considered a deviation.

Rescue medication:

Benzodiazepines could be used as rescue medication during the initial drug-free period of at least 5 days as needed, during the rest of the study no more than twice a week.

Objectives

The primary study objective was to demonstrate that monotherapy with ESL (800 to 1600 mg QD) was not inferior to monotherapy with controlled-release carbamazepine (CBZ-CR; 200-600 mg BID) in adults (≥ 18 years) with newly diagnosed epilepsy experiencing partial-onset seizures.

Secondary objectives were to demonstrate the efficacy, safety and PK of ESL in this population at the doses used

Outcomes / endpoints

The primary efficacy variable was the proportion of subjects in the Per Protocol (PP) set who were classified as seizure-free for the entire 26-week Evaluation Period at the last evaluated dose level. Subjects who dropped out during this 26-week period were considered as non-seizure-free. Subjects who dropped out during the Titration/Stabilisation Period were considered as non-seizure-free at the last received dose level.

Each subject was instructed to keep a seizure diary in their eDiary and record all seizures by date, time of occurrence and duration throughout the study. The subject was required to indicate whether or not a seizure had occurred on each day.

Seizures recorded by subjects in the eDiaries as well as seizures identified by the investigator were used. Both sources were consolidated, however, in case of discrepancies the final decision was with the investigator.

The secondary efficacy variables were:

- Proportion of seizure-free subjects during 1 year of treatment at the last evaluated dose.
- Time to first seizure at the last evaluated dose (treatment failure time).
- Time to treatment failure at the first evaluated dose, defined as the time of the first occurrence of 1 of the following during the Evaluation or Maintenance Periods of dose level A:
    - Seizure.
    - Withdrawal of investigational medicinal product due to adverse events (AEs).
    - Withdrawal of investigational medicinal product due to lack of efficacy.
- Treatment retention time, defined as the time of the first occurrence of 1 of the following:
    - Withdrawal of investigational medicinal product due to AEs.
    - Withdrawal of investigational medicinal product due to lack of efficacy.
- Seizure type and duration of the first seizure during the Evaluation Period and all seizures that led to up-titration (i.e. the last seizure in the respective dose) and for the last seizure before discontinuation in any study period up to the end of the Evaluation Period.
- Time to withdrawal for any reason at the last evaluated dose.
- dose level at which subjects reached 26-week seizure freedom (dose-response relationship)
- Seizure rate during the Titration/Stabilisation Periods of dose level A, of any dose level and of last evaluated dose and during the Evaluation Period of the last evaluated dose.
- Changes in quality of life (QOL) assessed using the validated QOLIE-31 survey (final scores and T-scores for overall score, global assessment and subscores covering emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects and overall QOL). Paper-based questionnaires were completed by the subjects.

Sample size

The sample size of 360 subjects per treatment group was estimated to have a power of at least 90% to establish non-inferiority of ESL compared to CBZ-CR using a non-inferiority margin of -12%, with the assumption that the proportion of subjects who were seizure free for 26 weeks was 60% for both

treatments. In order to achieve 360 evaluable subjects per treatment group in the PP set (the primary analysis population) and assuming a rate of 20% of subjects would not qualify for the PP set, 450 subjects were initially planned to be randomised per treatment group. However, during the continuous monitoring of protocol violations, it appeared that the actual rates of subjects not qualifying for the PP set tended to be lower than estimated. The revised rate was estimated to be below 12%, and thus the minimal number of randomised subjects per treatment group was decreased to 407 subjects.

Randomisation

At Visit A1, subjects who met the selection criteria were randomly allocated in a 1:1 ratio to either ESL or CBZ-CR using Interactive Web Response System. The randomisation schedule linked sequential numbers to treatment codes allocated at random. Complete blocks were assigned dynamically to each study site to achieve balanced assignment of treatment groups within a site. A site stratified block randomisation was used with a block size of 4. Within each block, the same number of subjects was allocated to each of the 2 treatment groups. The block size was not revealed to the site.

Blinding (masking)

Due to the different appearance of the ESL and CBZ-CR tablets, all tablets were identically over-encapsulated to ensure double-blind conditions. Treatment was taken orally in a double-blind setting with placebo tablets as appropriate.

Investigational medicinal products were blinded and the randomisation schedule and the allocation to treatment groups were not known to the investigator, the sponsor or any other person involved in the conduct of the study, except in case of an emergency.

Statistical methods

Efficacy analyses were primarily presented for the PP set and the full analysis set (FAS) and the last evaluated pooled dose. Selected analyses were repeated for the PP Subset (SPP).

- FAS: Included all subjects randomised and treated with at least 1 dose of investigational medicinal product after randomisation. Following the intention-to-treat principle, all subjects were analysed according to the treatment group to which they were randomised.
- PP set: Included all subjects from the FAS excluding subjects with major protocol deviations. All subjects were analysed according to the treatment group to which they were randomised.
- SPP: Included all subjects of the PP set excluding all subjects withdrawn from the study before reaching the end of the 26-week Evaluation Period for any reasons not linked to efficacy.

In general, continuous variables were summarised using descriptive statistics, i.e. number of subjects in the respective analysis sets, number of subjects with data, number of subjects with missing values, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum.

Categorical variables were summarised using frequency counts and percentages. In addition, the number of subjects with missing values was presented.

Events or therapies with an end date after the cut-off date were reported as ongoing as this was the status at the time of cut-off.

The baseline value was defined as the last available measurement at or before the Baseline Day (defined as the day of first intake of dose level A).

One primary analysis was planned for the study, to be performed after the primary endpoint was available for all subjects and the database was locked on 17-Nov-2015. The cut-off date for this analysis was 24-Sep-2015.

Non-inferiority (NI) of ESL to CBZ-CR for the proportion of subjects with 26-week seizure freedom was considered shown if the one-sided 97.5% confidence interval (CI) for absolute difference in proportions did not exceed the pre-specified NI margin of -12% in the PP set. This corresponded to the requirement that the lower limit of the two-sided 95% CI was greater than or equal to -12%. If NI was shown in the PP set, a subsequent test for NI was to be performed in the FAS. If NI could not be shown in the PP set, the sequential testing procedure was to be stopped. If NI was shown on the FAS, a subsequent test for superiority was to be performed one-sided with a 2.5% significance level in the FAS.

The primary analyses were based on a logistic regression with factors 'last evaluated pooled dose' and 'region'. The difference in proportions stratified by geographical region was estimated by the average risk difference (ARD) over the different regions and was estimated from the coefficients of the specified logistic regression model with treatment and region as main factors. The results of the logistic regression model including the estimates for the regression coefficients, the predicted probability to be seizure-free, the average risk difference and the corresponding CI were tabulated by last evaluated dose. Odds ratios and corresponding CIs were presented in addition, as appropriate.

For the primary efficacy analysis and the majority of secondary analysis, dropouts which did not complete the respective analysis period were considered as non-seizure free. The assumption was that missing data which were primarily caused by a dropout may have been related to treatment failure and thus these subjects were considered treatment failures. Depending on the dropout rate of the individual treatment groups, this approach may have been conservative or not for the comparison of the 2 treatment groups.

In order to evaluate the robustness of the methodology, the Mantel-Haenszel estimate of the common risk difference was presented together with corresponding 95% CI (using Sato's variance estimator) as well as the summary score estimate (Agresti) of the common risk difference together with the stratified Newcombe 95% CI. Unadjusted effect sizes and their corresponding 95% CIs were presented based on the Farington Manning test in addition to evaluate the influence of the regional adjustment on the treatment effect. In addition, potential interaction effects were evaluated by repeating the logistic regression model including the interaction term of treatment and region. The influence of age was evaluated by repeating the logistic regression model including age (years) as a covariate and including the interaction term of treatment and age.

The 1-year treatment effect was analysed using the same methodology as for the primary analysis. It was assumed that only dropouts due to an AE or lack of efficacy were related to a potential treatment failure. Other subjects and especially those subjects who did not complete the 1-year period because of insufficient observation time were assumed to be seizure-free.

The relative risk difference (RRD) to be seizure-free and its corresponding 95% CI was presented for the Evaluation Period as well as for the 1-year proportion of seizure-free subjects and compared against the NI margin of -20% as exploratory analyses.

The treatment failure time, defined as the time to first seizure at the last evaluated dose, was analysed and presented descriptively by means of the Kaplan-Meier estimate for the failure time, log-rank test, and a Cox proportional hazards model with treatment and region as factors. Hazard ratios and corresponding 95% CIs were presented. Subjects were to be censored by their day of last treatment.

Time to treatment failure under dose level A, defined as the time of the first occurrence of a seizure or withdrawal of treatment due to an AE or due to lack of efficacy during the Evaluation/Maintenance Periods at dose level A, was presented by means of incidence curves by randomised treatment group.

The treatment retention time, defined as the time of the first occurrence of treatment withdrawal due to an AE or due to lack of efficacy, was analysed by randomised treatment group, and the Kaplan-Meier estimate for the failure time and log-rank test (with and without stratification by region) were presented.

The duration and seizure type of the last seizure that led to up-titration or discontinuation until the end of the Evaluation Period were presented descriptively for the last evaluated pooled and individual dose.

The time to withdrawal for any reason at the last evaluated dose was presented.

Due to the study design, a dose-response relationship could not be established by comparing the treatment effect with individual dose levels. Instead, the number and percentage of subjects were presented by the individual dose level of the last evaluated dose together with the seizure freedom rate by period. Due to the fact that the length of the Maintenance Period and Extension Phase could differ by subject, the exposure time of a subject could differ by several weeks or months. For this reason, an additional analysis focused on the seizure frequency adjusted for the exposure time until end of the Evaluation and Maintenance Periods and Extension Phase. The seizure frequency was expressed as frequency per subject-year.

The seizure occurrence rates of dose level A, of any dose level and of the last evaluated dose during the Titration/Stabilisation Periods and of the last evaluated dose during the Evaluation Period were summarised descriptively.

The derived QOLIE-31 scores were presented using descriptive statistics for each of the 7 multi-item scales (final scores and T-scores), for the overall score and for the global assessment for the QOLIE-31 at each visit by the last evaluated pooled dose.

Subgroup analyses

The primary efficacy analysis was repeated for subgroups described below and the logistic regression was repeated, including a treatment by subgroup interaction term. These analyses were repeated for the 1-year treatment effect.

Seizure frequency during the 3 months before baseline was considered strongly predictive of prognosis, and therefore subjects were classified as follows:

- ≤4 seizures during the last 3 months
- >4 seizures during the last 3 months

and as:

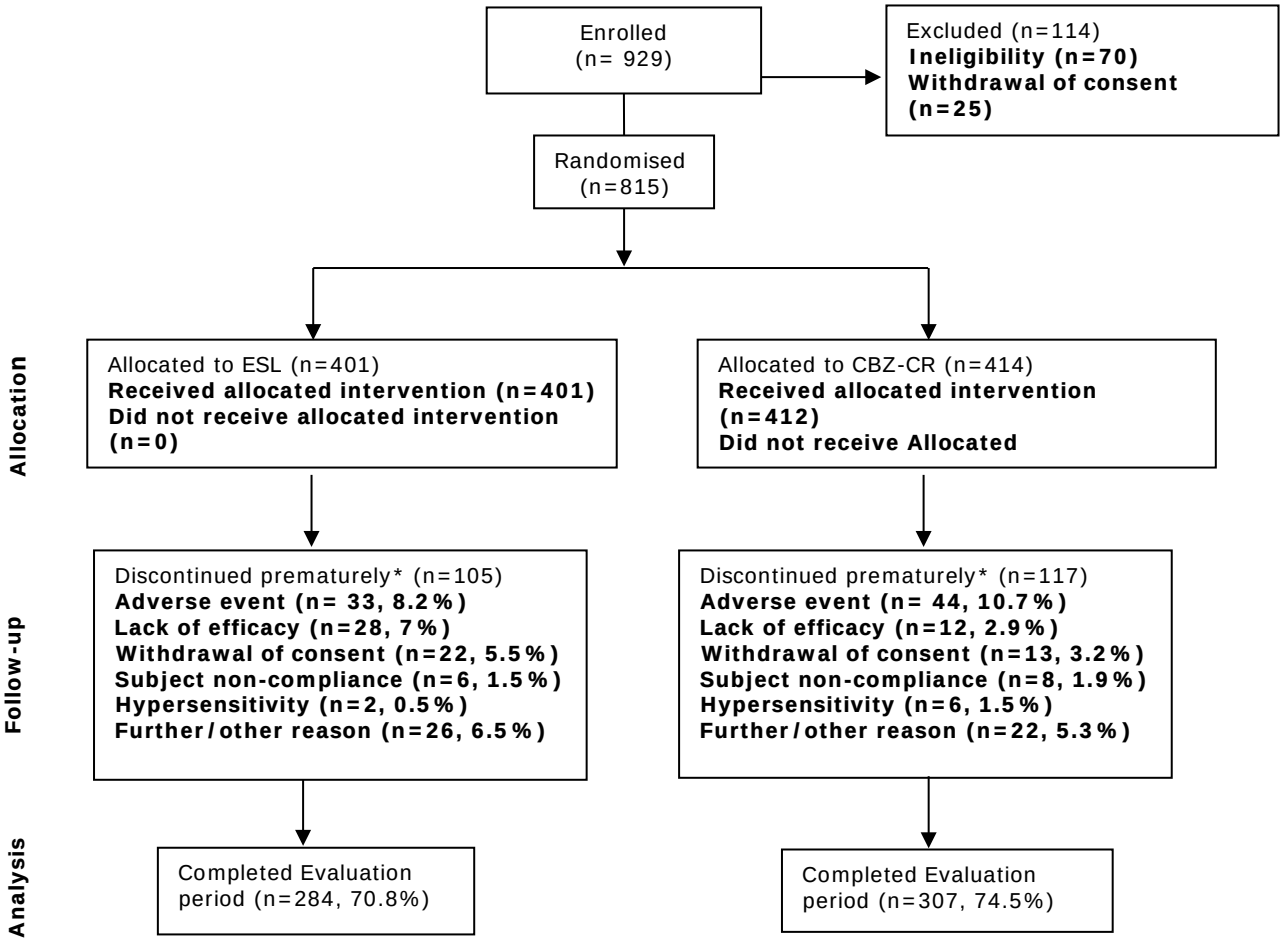
- ≤4 seizures during the last 12 months
- >4 seizures during the last 12 months

In addition, subjects were classified by:

- Baseline seizure type. In case that different seizure types had been reported for a subject, the worst type before baseline as selected:
    - III. Unclassified/Other
    - I.A. Simple partial
    - I.B. Complex partial
    - I.C. Partial evolving to secondarily generalised seizures
- Age group: <65 years / ≥65 years
- Previous treatment with AEDs in the 15 days before randomisation that were stopped before first IMP intake: Yes/No

2.4.2.2. Results

Participant flow



* before end of 26 weeks evaluation period.

At the time of the data cut-off for this application, the Maintenance Period was still ongoing, and was completed by 59.9% of ESL subjects and 64.1% of CBZ-CR subjects.

The majority of subjects (ESL: 271/401 [67.6%], CBZ-CR: 317/412 [76.9%]) remained on treatment at dose level A and thus the number of subjects that needed up-titration to higher dose levels was relatively small: at dose level B, 70/401 subjects (17.5%) were treated with ESL and 61/412 (14.8%) with CBZ-CR and at dose level C, 60/401 subjects (15.0%) were treated with ESL and 34/412 (8.3%) with CBZ-CR. Only 2 subjects (1 in each group) up titrated to a higher dose despite being seizure free.

Of the 401 ESL subjects and 412 CBZ-CR subjects who received treatment, the majority of subjects in both groups (70.8% in the ESL group and 74.5% in the CBZ-CR group) completed the 26-week Evaluation Period. By the last evaluated dose, the majority of subjects completed the Evaluation Period at dose level A (ESL: 79.7%, CBZ-CR: 76.7%) and dose level B (ESL: 61.4%, CBZ-CR: 78.7%), and slightly fewer subjects completed at dose level C (ESL: 41.7%, CBZ-CR: 47.1%).

The most commonly reported primary reasons for premature discontinuation before the end of the Evaluation Period, as classified by the investigator, were AEs, lack of efficacy (i.e. seizure at dose level C), and withdrawal of consent. While fewer CBZ-CR subjects (2.9%) prematurely discontinued due to lack of efficacy (i.e. seizure at dose level C) compared to ESL subjects (7.0%), more CBZ-CR subjects (10.7%) discontinued due to AEs than ESL subjects (8.2%).

Recruitment

A total of 135 study centres in 31 countries (Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, India, Israel, Argentina, Brazil, Chile and Peru) participated in the study.

The first subject was enrolled on 27-Jan-2011, date of data-cut-off: 24-Sep-2015.

Conduct of the study

At the time of the reporting there were 2 protocol amendments to study 311:

Protocol amendment 1 (29 Jun 2012)

- The mandatory 8-hour fasting period prior to blood sampling procedure was removed (analytes to be measured were not relevant for any selection criteria or any study endpoint).
- Need to administer the morning doses at study sites (at study visits) was removed.
- Due to recruitment issues, the limitation of benzodiazepines use for a maximum of 2 days during the 5-day drug-free period between the Screening Visit (Visit 1) and the Randomisation Visit (Visit A1) was removed. The possible carry-over effect of benzodiazepines would not be different compared with administration on only 2 days. In addition, seizures during the first 2 weeks of treatment will not be considered for the study endpoints, and any possible carry-over effect would therefore not impact the study endpoints.
- Further, clarification and specification on study procedures.

Protocol amendment 2 (27 Mar 2015)

The objective of this amendment was to clarify the end of the double-blind study, permitting some subjects to terminate early or even skip their Maintenance Phase, so that the open-label extension study, which was performed under a separate protocol, could commence in due time. Under this amendments, subjects were allowed to end the double-blind study after at least 54 weeks of double-blind treatment with the latter being potentially at different doses but still after end of the evaluation period. This amendment had thus no impact on the on the primary evaluation period.

According to the updated European Medicines Agency CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, monotherapy studies should have a minimum duration of 1 year. The protocol specified a 1-year treatment duration on the same dose, which was not required by the guideline and was considered to unduly delay the termination of the study.

As soon as the stop conditions were met, a Final endpoint visit was scheduled within 42 days for all subjects. After this, the subjects continued attending Extension phase visits every 3 months. As soon as the regular unblinding took place, the last visit was to be held for all subjects within 42 days.

Due to protocol amendment 2, the Down-titration and Follow-up Phases were only part of the statistical analyses if subjects discontinued early, the down-titration and follow-up phases of all other subjects were after the cut-off date.

Changes from the protocol in the planned analyses:

Among others, the following criteria for exclusion of subjects from the PP set were changed:

The time period for “History of newly diagnosed epilepsy with at least 2 well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalisation) with clear focal

origin" was extended from 12 months to 13 months in order to ease the classification of subjects with partial dates.

The time period for "No seizure during the previous 3 months" was extended to previous 4 months for the same reason as above.

The criterion "Treated with investigational medicinal product not according to titration regimen" was deleted because it was considered a minor deviation. Some subjects were titrated to a higher dose even though they were seizure free until end of evaluation period. The reason was that the visit was delayed and the investigator evaluated all seizures until the visit. The subjects were analysed using the data of the last evaluated dose.

The criterion "Poor compliance for completion of the eDiary" was deleted because the primary analysis was based on the seizures as reported by the investigator.

Major Protocol violations:

Major protocol violations were reported for 13 ESL subjects (3.2%) and 15 CBZ-CR subjects (3.6%). These subjects were excluded from the PP set. The most common major protocol violations were incorrect enrolment of subjects who did not meet the inclusion criterion providing that epilepsy was diagnosed more than 13 months prior to Visit 1 or enrolment of subjects who met exclusion criteria (e.g. former or current use of >1 AED for >2 weeks before Visit 1; previous regular use of ESL or CBZ), intake of prohibited therapies and poor compliance for taking investigational medicinal product.

Baseline data

Baseline subject demographics are summarised in Table 2.

The treatment groups were overall balanced with respect to demographic parameters. The majority of subjects was < 65 years, only 6.7% (N=27) of ESL subjects and 8.5% (N=35) of CBZ-CR subjects were 65 years or older. Most subjects (~80%) were Caucasian. There were slightly more male subjects included than female.

Table 2 - Baseline demographics – Safety Set/FAS

Characteristic	ESL (N=401)	CBZ-CR (N=412)	Total (N=813)
Gender, n (%)			
Male	228 (56.9)	220 (53.4)	448 (55.1)
Female	173 (43.1)	192 (46.6)	365 (44.9)
Age (years)			
n	401	412	813
Mean (SD)	37.6 (15.79)	38.7 (16.29)	38.2 (16.05)
Min	18	18	18
Max	85	81	85
Age group, n (%)			
18 to <50 years	305 (76.1)	294 (71.4)	599 (73.7)
50 to <65 years	69 (17.2)	83 (20.1)	152 (18.7)
65 to <85 years	26 (6.5)	35 (8.5)	61 (7.5)
≥85 years	1 (0.2)	0 (0.0)	1 (0.1)
Ethnicity, n (%)			
Caucasian (White)	322 (80.3)	336 (81.6)	658 (80.9)
African (Black)	2 (0.5)	4 (1.0)	6 (0.7)
Asian	37 (9.2)	36 (8.7)	73 (9.0)
Other	40 (10.0)	36 (8.7)	76 (9.3)
Body mass index (kg/m^2)			
n	401	411	812
Mean (SD)	25.2 (4.81)	25.4 (5.08)	25.3 (4.95)
Min	15	15	15
Max	47	47	47
Body mass index group, n (%)			
<18 kg/m^2	17 (4.2)	20 (4.9)	37 (4.6)
18 to 30 kg/m^2	321 (80.0)	322 (78.2)	643 (79.1)
>30 kg/m^2	63 (15.7)	69 (16.7)	132 (16.2)
Missing	0 (0.0)	1 (0.2)	1 (0.1)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = number of subjects in analysis set; n = number of subjects with data; SD = standard deviation.

Disease characteristics

The mean age of onset of epilepsy was 37.3 years in the ESL group and 38.4 years in the CBZ-CR group.

The most frequently reported aetiologies of the disease were cranial trauma/injuries (8.7% in ESL and 10.9% in CBZ-CR) and cerebrovascular disease (8.5% in ESL and 8.3% in CBZ-CR). The aetiology was reported as unknown for 66.8% of ESL subjects and 61.9% of CBZ-CR subjects. At least 91% of subjects in either treatment group had no family history of epilepsy.

During the last year prior to enrolment in the study, the mean number of seizures experienced by subjects (FAS) was similar between the treatment groups with 20.1 in the ESL group (range: 2 to 836) and 19.0 in the CBZ-CR group (range: 1 to 999). The seizures were mainly simple partial (mean of 8.5 seizures in the ESL group and 9.1 in the CBZ-CR group) and complex seizures (mean of 9.8 seizures in the ESL group and 8.3 in the CBZ-CR group).

Table 3 provides an overview of the baseline seizure frequency at the different doses given for the PP set (used for the primary efficacy analyses).

Table 3 - Baseline seizure frequency by last evaluated individual dose during the last year and during the last 3 months – PP set

Characteristic	ESL				CBZ-CR			
	800 mg QD (N=262)	1200 mg QD (N=69)	1600 mg QD (N=57)	Total (N=388)	200 mg BID (N=304)	400 mg BID (N=60)	600 mg BID (N=33)	Total (N=397)
Number of seizures during last year								
Total seizures								
n	262	69	57	388	304	60	33	397
Mean (SD)	10.1 (23.35)	52.9 (138.06)	28.9 (47.15)	20.5 (65.64)	12.4 (32.29)	20.2 (41.76)	51.6 (97.20)	16.8 (44.03)
Median (Min, Max)	3.0 (2, 201)	5.0 (2, 836)	7.0 (2, 240)	4.0 (2, 836)	4.0 (2, 286)	5.0 (2, 270)	20.0 (2, 450)	4.0 (2, 450)
Simple partial								
n	262	68	57	387	304	60	33	397
Mean (SD)	4.6 (17.55)	23.0 (101.45)	10.1 (28.82)	8.7 (46.50)	5.5 (19.65)	7.5 (15.93)	17.2 (35.33)	6.8 (21.08)
Median (Min, Max)	0.0 (0, 200)	0.0 (0, 792)	0.0 (0, 150)	0.0 (0, 792)	0.0 (0, 200)	0.0 (0, 80)	0.0 (0, 150)	0.0 (0, 200)
Complex partial								
n	262	69	57	388	304	60	33	397
Mean (SD)	3.8 (16.06)	28.0 (96.21)	16.7 (41.30)	10.0 (46.24)	5.4 (23.40)	10.5 (40.04)	32.9 (80.40)	8.4 (35.19)
Median (Min, Max)	0.0 (0, 195)	1.0 (0, 730)	1.0 (0, 240)	0.0 (0, 730)	0.0 (0, 260)	0.0 (0, 270)	2.0 (0, 360)	0.0 (0, 360)
Partial evolving to secondarily generalised								
n	262	69	57	388	304	60	33	397
Mean (SD)	1.7 (2.47)	2.2 (3.47)	2.1 (3.19)	1.8 (2.78)	1.5 (1.59)	2.2 (2.79)	1.5 (2.03)	1.6 (1.87)
Median (Min, Max)	1.0 (0, 32)	1.0 (0, 24)	1.0 (0, 15)	1.0 (0, 32)	1.0 (0, 9)	1.0 (0, 12)	1.0 (0, 7)	1.0 (0, 12)
Unclassified								
n	262	69	57	388	304	60	33	397
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.06)	0.0 (0.00)	0.0 (0.00)	0.0 (0.05)
Median (Min, Max)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 1)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 1)
Number of seizures during previous 3 months								
Total seizures								
n	262	69	57	388	304	60	33	397

Characteristic	ESL				CBZ-CR			
	800 mg QD (N=262)	1200 mg QD (N=69)	1600 mg QD (N=57)	Total (N=388)	200 mg BID (N=304)	400 mg BID (N=60)	600 mg BID (N=33)	Total (N=397)
Mean (SD)	4.5 (7.40)	16.7 (36.39)	10.8 (15.35)	7.6 (18.07)	5.7 (16.36)	7.7 (12.15)	15.4 (19.19)	6.8 (16.24)
Median (Min, Max)	2.0 (1, 50)	3.0 (1, 215)	3.0 (1, 60)	2.0 (1, 215)	2.0 (1, 230)	2.5 (1, 65)	7.0 (1, 90)	2.0 (1, 230)
Simple partial								
n	262	69	57	388	304	60	33	397
Mean (SD)	1.9 (5.62)	6.9 (26.47)	3.2 (9.82)	3.0 (12.72)	2.1 (5.93)	2.9 (5.97)	5.2 (9.55)	2.5 (6.35)
Median (Min, Max)	0.0 (0, 50)	0.0 (0, 198)	0.0 (0, 52)	0.0 (0, 198)	0.0 (0, 47)	0.0 (0, 30)	0.0 (0, 40)	0.0 (0, 47)
Complex partial								
n	262	69	57	388	304	60	33	397
Mean (SD)	1.5 (5.13)	8.7 (25.64)	6.2 (13.49)	3.5 (12.97)	2.6 (15.29)	3.5 (11.22)	8.9 (18.36)	3.3 (15.10)
Median (Min, Max)	0.0 (0, 45)	1.0 (0, 180)	0.0 (0, 60)	0.0 (0, 180)	0.0 (0, 230)	0.0 (0, 65)	1.0 (0, 90)	0.0 (0, 230)
Partial evolving to secondarily generalised								
n	262	69	57	388	304	60	33	397
Mean (SD)	1.0 (1.15)	1.2 (1.51)	1.3 (1.69)	1.1 (1.31)	0.9 (0.93)	1.3 (1.81)	1.2 (2.02)	1.0 (1.23)
Median (Min, Max)	1.0 (0, 9)	1.0 (0, 8)	1.0 (0, 9)	1.0 (0, 9)	1.0 (0, 6)	1.0 (0, 11)	0.0 (0, 7)	1.0 (0, 11)
Unclassified								
n	262	69	57	388	304	60	33	397
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median (Min, Max)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)

BID = twice daily; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; Max = maximum; Min = minimum; N = number of subjects in analysis set; n = number of subjects with data; PP = Per Protocol; QD = once daily; SD = standard deviation

The treatment groups were generally balanced with respect to epilepsy disease characteristics.
In the PP set, in both treatment groups a median of 4 seizures was experienced within 1 year prior to enrolment and a median of 2 seizures was experienced within 3 months prior to enrolment. However, whereas the total baseline seizure frequency was relatively similar in both treatment groups, baseline seizure frequency by dose level was similar at dose level A, it was higher in the ESL group at dose level B and higher in the CBZ-CR group at dose level C.

Most subjects had concomitant medical conditions with a similar incidence in each of the treatment groups (73.1% of ESL and 71.6% of CBZ-CR subjects), including nervous system disorders, metabolism and nutrition disorders and vascular disorders. The most commonly reported concomitant medical conditions (>5% of subjects in either treatment group) were hypertension, obesity and headache.

Previous and concomitant medication

Previous non-AED therapies were used by 33.7% of ESL subjects and 35.0% of CBZ-CR subjects and the majority of subjects in either group used a concomitant therapy (ESL: 70.6% of subjects, CBZ-CR: 69.4% of subjects). The most frequently used concomitant therapies (>15% of subjects in either treatment group) were anti-inflammatory and anti-rheumatic products (22.9% of ESL subjects and 22.6% of CBZ-CR subjects), analgesics (20.9% of ESL subjects and 25.2% of CBZ-CR subjects), AEDs (20.4% of ESL subjects and 13.3% of CBZ-CR subjects), agents acting on the renin-angiotensin system (14.5% of ESL subjects and 18.7% of CBZ-CR subjects) and anti-bacterials for systemic use (14.7% of ESL subjects and 18.2% of CBZ-CR subjects).

The use of different previous or concomitant non-AED therapies was generally comparable between treatment groups.

Previous and concomitant AED therapy

Previous AEDs (allowed for a maximum of 2 weeks for a single AED) had been used by similar proportions of subjects in both treatment groups, i.e. 17.7% of ESL and 16.7% CBZ-CR subjects. The most frequently used previous AEDs (≥2% of subjects in either the ESL or CBZ-CR group) included carbamazepine, clobazam, clonazepam, levetiracetam, phenytoin and valproic acid with similar percentages of subjects in each treatment group.

Concomitant AEDs were used by 25.7% of ESL subjects and 18.0% CBZ-CR subjects. The difference mainly derives from a higher percentage of subjects using AEDs in the ESL group compared to CBZ-CR at dose level B (38.6% versus 19.7%) and dose level C (46.7% versus 35.3%). Most of these were not considered protocol deviations including use of Zolpidem and Zopiclone, if an AED was started at or after Early Discontinuation Visit, if an AED was started at or after the last investigational medicinal product intake, if a new AED was started during a window of 7 days before the start of down-titration, and benzodiazepines ≤twice a week, all of which were allowed according to protocol.

The incidences of concomitant AEDs including carboxamide derivatives, respectively in the FAS are given in the following table. Respective results for the PP set were comparable.

Table 4 – Any Concomitant AED (FAS/Safety Set)

Drug Class / Preferred Drug Name	Statistic	ESL (N=401)	CBZ-CR (N=412)	Total (N=813)
Any concomitant AED	n (%)	103 (25.7)	74 (18.0)	177 (21.8)
Antiepileptics	n (%)	82 (20.4)	55 (13.3)	137 (16.9)
ANTIEPILEPTICS	n (%)	1 (0.2)	-	1 (0.1)
CARBAMAZEPINE	n (%)	20 (5.0)	13 (3.2)	33 (4.1)
CLOBAZAM	n (%)	5 (1.2)	6 (1.5)	11 (1.4)
CLONAZEPAM	n (%)	3 (0.7)	2 (0.5)	5 (0.6)
ESLICARBAZEPINE	n (%)	8 (2.0)	1 (0.2)	9 (1.1)
GAMMA-AMINOBUTYRIC ACID	n (%)	-	1 (0.2)	1 (0.1)
LACOSAMIDE	n (%)	3 (0.7)	-	3 (0.4)
LAMOTRIGINE	n (%)	6 (1.5)	7 (1.7)	13 (1.6)
LEVETIRACETAM	n (%)	27 (6.7)	17 (4.1)	44 (5.4)
LORAZEPAM	n (%)	2 (0.5)	2 (0.5)	4 (0.5)
MAGNESIUM SULFATE	n (%)	3 (0.7)	-	3 (0.4)
OXCARBAZEPINE	n (%)	4 (1.0)	4 (1.0)	8 (1.0)
PHENOBARBITAL	n (%)	2 (0.5)	1 (0.2)	3 (0.4)
PHENYTOIN	n (%)	2 (0.5)	1 (0.2)	3 (0.4)
TOPIRAMATE	n (%)	-	2 (0.5)	2 (0.2)
VALPROATE SODIUM W/VALPROIC ACID	n (%)	2 (0.5)	1 (0.2)	3 (0.4)
VALPROIC ACID	n (%)	4 (1.0)	4 (1.0)	8 (1.0)
ZONISAMIDE	n (%)	1 (0.2)	-	1 (0.1)
Benzodiazepine derivatives	n (%)	35 (8.7)	27 (6.6)	62 (7.6)
ALPRAZOLAM	n (%)	2 (0.5)	2 (0.5)	4 (0.5)
BROMAZEPAM	n (%)	2 (0.5)	5 (1.2)	7 (0.9)
BROTIZOLAM	n (%)	-	1 (0.2)	1 (0.1)
CLOBAZAM	n (%)	1 (0.2)	-	1 (0.1)
CLONAZEPAM	n (%)	1 (0.2)	2 (0.5)	3 (0.4)
DIAZEPAM	n (%)	16 (4.0)	6 (1.5)	22 (2.7)
LORAZEPAM	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
MEDAZEPAM	n (%)	1 (0.2)	-	1 (0.1)
MIDAZOLAM	n (%)	3 (0.7)	6 (1.5)	9 (1.1)
MIDAZOLAM HYDROCHLORIDE	n (%)	-	1 (0.2)	1 (0.1)
OXAZEPAM	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
PHENAZEPAM	n (%)	3 (0.7)	-	3 (0.4)
TRIAZOLAM	n (%)	-	1 (0.2)	1 (0.1)
ZOLPIDEM	n (%)	3 (0.7)	7 (1.7)	10 (1.2)
ZOPICLONE	n (%)	4 (1.0)	1 (0.2)	5 (0.6)
Barbiturates	n (%)	1 (0.2)	-	1 (0.1)
THIOPENTAL	n (%)	1 (0.2)	-	1 (0.1)

AED = anti-epileptic drug; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; FAS = Full Analysis Set; N = number of subjects in analysis set; n = number of subjects with data.
Note: Includes therapies started during the Down-titration Phase for discontinued subjects.

Treatment compliance

Overall compliance to treatment administration was good with 99.3% compliance in both treatment groups until the end of the Evaluation Period and approximately 99.6% compliance until the end of the Maintenance Period. The majority of subjects in both groups were within the 80% to 120% compliance category during both the Evaluation (89.8 % of both treatment groups) and Maintenance Periods (68.8% of ESL and 72.1% of CBZ-CR patients).

Numbers analysed

The Safety Set and FAS included all 401 subjects (all randomised subjects) in the ESL group and 412 subjects (99.5% of randomised subjects) in the CBZ-CR group who received treatment. Major protocol violations were reported for 13 ESL subjects (3.2%) and 15 CBZ-CR subjects (3.6%). These subjects were excluded from the PP set, which comprised 388 subjects (96.8%) from the ESL group and 397 subjects (95.9%) from the CBZ-CR group. The SPP set comprised 316 ESL subjects (78.8%) and 326 CBZ-CR subjects (78.7%).

Table 5 – Study 311 – Analysis Populations

Population (analysis set)	Number (%) of subjects		
	ESL (N=401)	CBZ-CR (N=414)	Total (N=815)
Randomised	401 (100)	414 (100)	815 (100)
Safety Set	401 (100)	412 (99.5)	813 (99.8)
FAS	401 (100)	412 (99.5)	813 (99.8)
PP Set	388 (96.8)	397 (95.9)	785 (96.3)
SPP	316 (78.8)	326 (78.7)	642 (78.8)

Outcomes and estimation

- Primary efficacy analysis

The primary efficacy variable was the proportion of subjects in the PP set classified as seizure-free for the entire 26-week Evaluation Period at the last received dose level. Subjects who dropped out during this 26-week period were considered non-seizure-free.

As shown in Table 6, in the PP set, a similar proportion of subjects were classified as seizure-free for the entire 26-week Evaluation Period at the last evaluated dose in the ESL group (276/388, 71.1%) and the CBZ-CR group (300/397, 75.6%). The lower limit of the 95% CI (-10.30%) was within the predefined non-inferiority margin of -12%.

Table 6 - Seizure freedom during the Evaluation Period – Average Risk Difference (PP set)

Statistic	ESL (N=388)	CBZ-CR (N=397)
Number (%) of seizure-free subjects	276 (71.1)	300 (75.6)
Difference of ESL – CBZ-CR		
ARD (%)	-4.28	
SE	3.07	
95% CI	(-10.30; 1.74)	

ARD = average risk difference of ESL – CBZ-CR to be seizure-free stratified by region (estimated from the logistic regression coefficients); CBZ-CR = carbamazepine controlled-release; CI = confidence interval; ESL = eslicarbazepine acetate; N = number of subjects in analysis set; PP = Per Protocol; SE = standard error of the estimate (Multivariate Delta Method).

Note: Confidence interval non-inferiority margin = -12%, i.e. ESL is assumed to be non-inferior to CBZ-CR if the lower limit of the CI ≥-12%.

The results in the FAS were similar to those of the PP set with 70.8% (284/401) ESL subjects and 74.0% (305/412) CBZ-CR subjects classified as seizure-free during the entire 26-week Evaluation Period. The lower limit of the 95% CI (-9.04) was larger than -12%.

ESL was not found to be superior to CBZ-CR for the proportion of seizure-free subjects in the FAS during the Evaluation Period, because the lower limit of the two-sided 95% CI was below 0.

Results for seizure freedom during the Evaluation Period based on the logistic regression with region as factor, supported the ARD analysis in the PP set (odds ratio: 0.793, 95% CI: 0.572; 1.100) and the FAS (odds ratio: 0.849, 95% CI: 0.618; 1.167).

Sensitivity analyses:

In the SPP set, 87.3% (276/316) ESL subjects and 92.0% (300/326) CBZ-CR subjects classified as seizure-free during the entire 26-week Evaluation Period. The lower limit of the 95% CI of the ARD was -9.13% and thus within the predefined NI margin. This was further supported by the results based on the logistic regression with region as factor (odd ratio: 0.598, 95% CI: 0.351; 1.016).

Comparable results were derived from the analyses of seizure-free subjects during the Evaluation period based on the Mantel-Haenszel estimate and the summary score estimate of the Common Risk Difference with Newcombe 95% CI in the PP set (lower limit of Mantel-Haenszel 95% CI: -10.32, lower limit of Newcombe 95% CI: -10.23) and in the FAS (lower limit of Mantel-Haenszel 95% CI: -9.06, lower limit of Newcombe 95% CI: -9.14). Likewise, the un-stratified Farrington Manning Test supported the primary analysis in both the PP set (95% CI: -10.61; 1.74, p=0.0082) and the FAS (95% CI: -9.34; 2.93, p=0.0025).

No interaction was indicated between treatment and region when included in the logistic regression model for seizure freedom during the Evaluation Period in the PP set (p=0.4930) or the FAS (p=0.5124). Between regions, the predicted probability to be seizure-free during the Evaluation Period ranged from approximately 60% to approximately 85% in both the PP set and the FAS. In the SPP set, the predicted probability to be seizure-free showed less variation between regions and was higher than in the PP set and FAS, ranging from approximately 80% to approximately 95%.

There was no interaction between age and treatment (PP set: p=0.2811, FAS: p=0.2785).

- Secondary efficacy analyses

Proportion of seizure-free subjects during 1 year (52 weeks) of treatment at the last evaluated dose

The primary analyses were repeated for the proportion of seizure-free subjects during 1 year of treatment. In the PP set, the lower limit of the ARD remained just within the non-inferiority margin of -12%. The results were similar in the FAS (lower limit of 95% CI: -11.07%).

Table 7 - Seizure Freedom during 1 Year of Treatment – ARD (PP set)

Statistic	ESL (N=388)	CBZ-CR (N=397)
Number (%) of seizure-free subjects	251 (64.7)	279 (70.3)
Non-inferiority test: difference of ESL – CBZ-CR		
ARD (%)	-5.46	
SE	3.28	
95% CI	(-11.88; 0.97)	

ARD = average risk difference of ESL – CBZ-to be seizure-free stratified by region (estimated from the logistic regression coefficients); CBZ-CR = carbamazepine controlled-release; CI = confidence interval (non-inferiority margin = -12%); ESL = eslicarbazepine acetate; N = number of subjects in analysis set; PP = Per Protocol; SE = standard error of the estimate (Multivariate Delta Method).

Sensitivity analyses:

Results for seizure freedom during 1 year of treatment based on the logistic regression with region as factor, supported the ARD analysis in the PP set (odds ratio: 0.772, 95% CI: 0.568; 1.048) and the FAS (odds ratio: 0.801, 95% CI: 0.595; 1.080).

Similar results were also obtained in the PP set based on the Mantel-Haenszel estimate (lower limit of Mantel-Haenszel 95% CI: -11.91) and the summary score estimate for the Common Risk Difference (lower limit of Newcombe 95% CI: -11.80). The results for the FAS were similar.

Between regions, the predicted probability to be seizure-free during 1 year of treatment ranged from approximately 50% to approximately 80% in both the PP set and the FAS.

As for the primary analysis, the risk difference to be seizure-free during 1 year of treatment, varied across regions. For the treatment groups overall disregarding stratification, based on the Farrington-Manning test, the 95% CI was within the -12% margin in the FAS (-11.32; 1.62, p=0.0151) and close to -12% in the PP set (95% CI: -12.11; 0.94, p=0.0270).

Based on the pre-specified threshold of 0.1, no interaction between region and treatment was found in the PP set (p=0.1771) or the FAS (p=0.2795), based on the logistic regression model. There was also no interaction between age and treatment (PP set: p=0.1465, FAS: p=0.1264).

The additional analyses in which subjects who did not complete the 1-year period were classified as non-seizure free, did not influence the outcome of the results; the lower level of the 95% CI remained within the pre-defined margin in the PP set and FAS based on the ARD and supporting logistic regression analyses, the Mantel-Haenszel estimate and summary score estimate for CRD and the Farrington Manning Test results.

Relative risk difference (RRD):

The explorative analyses of the RRD to be seizure-free (non-inferiority margin: -20%) were consistent with the primary analyses during the 26-week Evaluation Period (RDD: -5.87, 95% CI: -13.50, 2.44) as well as during the 1-year treatment period (RDD: -7.95, 95% CI: -16.50, 1.47) in the PP set. Similar results were obtained in the FAS.

Treatment failure time (i.e. time to 1st seizure at last evaluated dose)

At the end of the Evaluation Period (Day 182), the probability of treatment failure (i.e. risk of seizure) at the last evaluated dose was higher in the ESL group (0.12) than in the CBZ-CR group (0.06). The between treatment difference was -0.06 (95% CI: -0.0105; -0.021).

The time to first seizure was earlier in the ESL group, with an increased probability for treatment failure in the first 60 days of treatment compared to CBZ-CR (see following Figure). The Kaplan-Meier analyses were supported by the Cox proportional hazards model results (hazard ratio: 1.874, 95% CI: 1.348; 2.605). Consistent results were observed for the FAS.

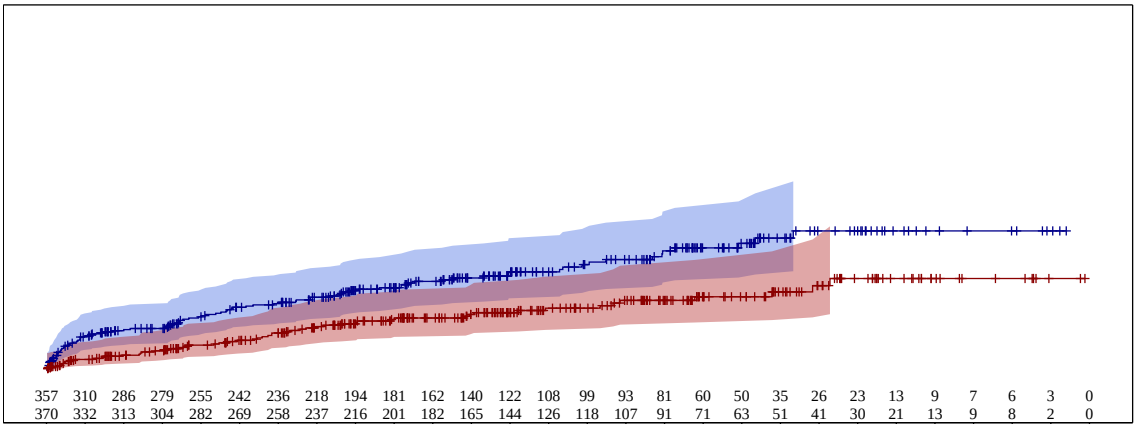


Figure 4 - Treatment failure time – Kaplan-Meier Product Limit Estimates (PP set)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; PP = Per Protocol

Note: The Kaplan-Meier Product Limit Estimate and equal precision 95% confidence bounds (Nair) are presented. Treatment failure is defined as the first occurrence of a seizure during the Evaluation or Maintenance Period. Days are relative to the start of the Evaluation Period of dose level A.

When only considering those subjects on dose level A (i.e. the dose on which most subjects remained during the study), the probability to have treatment failure (i.e. a seizure) was also higher in the first 60 days in the ESL group compared to the CBZ-CR group, but remained otherwise similar between treatment groups throughout the rest of the study.

Treatment retention time (i.e. time to withdrawal due to AEs or due to lack of efficacy)

The Kaplan-Meier curves for treatment retention time indicated that the ESL and CBZ-CR group had similar probability to withdraw up to Day 240 and that the ESL group had higher probability to withdraw from treatment from Day 240 (see following Figure).

After 1 year of treatment (Day 365), the probability estimate was 0.23 in the ESL group compared to 0.19 in the CBZ-CR group. After 2 years of treatment (Day 730), it was 0.34 in the ESL group and 0.29 in the CBZ-CR group. After 3 years of treatment (Day 1095), it was 0.42 in the ESL group and 0.34 in the CBZ-CR group. Similar results were observed for the FAS.

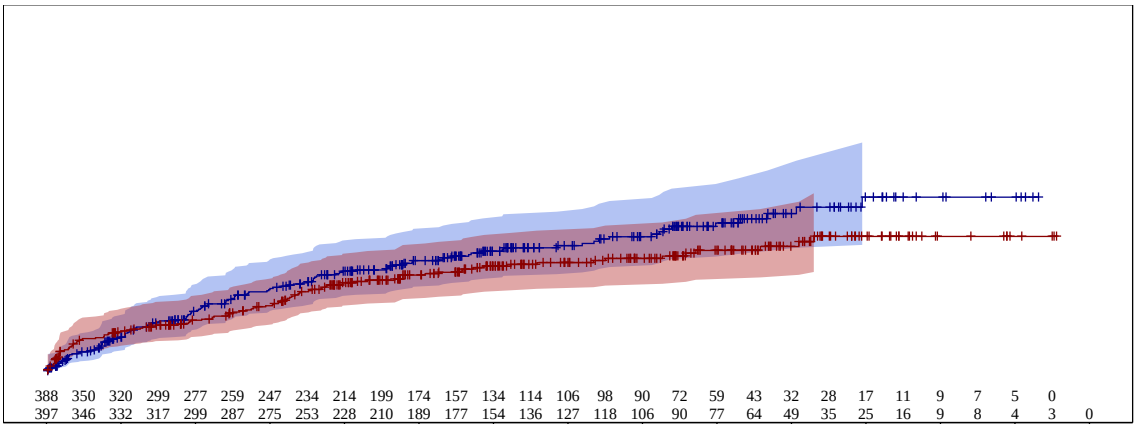


Figure 5 - Treatment Retention Time – Kaplan-Meier Product Limit Estimates by randomized treatment group (PP Set)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; PP = Per Protocol

Note: The Kaplan-Meier Product Limit Estimate and simultaneous equal precision 95% confidence bounds are presented.

Time to withdrawal (for any reason)

Overall, the percentage of subjects who discontinued from the study for any reason was similar between the treatment groups for the first 90 days and thereafter slightly higher in the ESL group compared to CBZ-CR over the remainder of the study in the PP set, FAS and Safety Set.

By last evaluated dose, the percentage of discontinuations was slightly higher in CBZ-CR subjects at dose level A, and higher for ESL subjects at dose level B and C. However, the results for dose level B and C should be interpreted with caution due to lower subject numbers.

Seizure duration and type

Seizure duration and type (of the last seizure before up-titration or discontinuation) during the evaluation period is presented in the following table.

Table 8 - Seizure duration and type of the last seizure before up-titration or discontinuation until the end of the Evaluation Period by randomized treatment group and last evaluated individual dose (FAS)

Last seizure	Number of subjects, n/M (%)					
	ESL			CBZ-CR		
	Dose level A (N=401)	Dose level B (N=130)	Dose level C (N=60)	Dose level A (N=412)	Dose level B (N=95)	Dose level C (N=34)
Duration						
Less than 30 s	29/141 (20.6)	18/74 (24.3)	7/27 (25.9)	17/101 (16.8)	8/40 (20.0)	2/12 (16.7)
30 s to 1 min	28/141 (19.9)	19/74 (25.7)	3/27 (11.1)	25/101 (24.8)	13/40 (32.5)	2/12 (16.7)
1 min to 5 min	38/141 (27.0)	11/74 (14.9)	5/27 (18.5)	28/101 (27.7)	10/40 (25.0)	2/12 (16.7)
More than 5 min	14/141 (9.9)	6/74 (8.1)	3/27 (11.1)	16/101 (15.8)	4/40 (10.0)	0/12 (0.0)

Last seizure	Number of subjects, n/M (%)					
	ESL			CBZ-CR		
	Dose level A (N=401)	Dose level B (N=130)	Dose level C (N=60)	Dose level A (N=412)	Dose level B (N=95)	Dose level C (N=34)
Unknown	13/141 (9.2)	8/74 (10.8)	4/27 (14.8)	8/101 (7.9)	2/40 (5.0)	2/12 (16.7)
Missing	19/141 (13.5)	12/74 (16.2)	5/27 (18.5)	7/101 (6.9)	3/40 (7.5)	4/12 (33.3)
Type						
Simple partial	34/141 (24.1)	17/74 (23.0)	4/27 (14.8)	41/101 (40.6)	16/40 (40.0)	4/12 (33.3)
Complex partial	59/141 (41.8)	33/74 (44.6)	12/27 (44.4)	33/101 (32.7)	17/40 (42.5)	5/12 (41.7)
Partial evolving to sec. generalised	43/141 (30.5)	24/74 (32.4)	11/27 (40.7)	23/101 (22.8)	4/40 (10.0)	2/12 (16.7)
Unclassifiable	3/141 (2.1)	0/74 (0.0)	0/27 (0.0)	3/101 (3.0)	1/40 (2.5)	1/12 (8.3)
Other	2/141 (1.4)	0/74 (0.0)	0/27 (0.0)	1/101 (1.0)	2/40 (5.0)	0/12 (0.0)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; n = number of subjects with last seizure of the respective duration/type; N = number of subjects in analysis set; M = number of subjects with a seizure before up-titration or discontinuation.

Note: Since subjects titrated to higher dose levels contribute to more than one dose level, subjects are counted more than once.

Information on duration of the respective seizures was unknown or missing in a noticeable percentage of subjects (i.e. approx. 23-33 % of ESL and 13-50 % of CBZ-CR subjects, respectively within the different dose levels).

Simple partial seizures were reported less in the ESL group (23%) than in the CBZ-CR group subjects (40%) while partial evolving to secondarily generalised seizures were reported by more ESL subjects (32%) than CBZ-CR subjects (19%); 43% (ESL) and 26% (CBZ-CR) were complex partial seizures.

Dose-response relationship: Dose level at which subjects reached 26-week seizure freedom

Due to the up-titration study design, it was not possible to compare the treatment effect by the individual dose levels or establish a dose relationship. Results are presented by the last evaluated individual dose level and subjects who were up-titrated were only analysed in the dose level that was their last evaluated dose.

Table 9 - Retention rate in seizure-free subjects by study period and last evaluated individual dose (PP Set)

Phase/Period	Number of subjects, n/M (%)					
	ESL			CBZ-CR		
	800 mg QD (N=262)	1200 mg QD (N=69)	1600 mg QD (N=57)	200 mg BID (N=304)	400 mg BID (N=60)	600 mg BID (N=33)
Main Treatment Phase	167/262 (63.7)	32/69 (46.4)	15/57 (26.3)	190/304 (62.5)	31/60 (51.7)	13/33 (39.4)
Titration Period	240/262 (91.6)	53/69 (76.8)	48/57 (84.2)	267/304 (87.8)	54/60 (90.0)	29/33 (87.9)
Stabilisation Period	235/254 (92.5)	55/67 (82.1)	50/53 (94.3)	272/291 (93.5)	52/59 (88.1)	28/33 (84.8)
Evaluation Period	210/246 (85.4)	43/58 (74.1)	23/53 (43.4)	237/285 (83.2)	47/53 (88.7)	16/32 (50.0)
Maintenance Period	183/210 (87.1)	34/43 (79.1)	16/23 (69.6)	212/238 (89.1)	34/47 (72.3)	13/16 (81.3)
Extension Phase	115/184 (62.5)	21/33 (63.6)	8/16 (50.0)	135/212 (63.7)	25/32 (78.1)	9/12 (75.0)

BID = twice daily; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; M = number of subjects entering the respective period/phase at the last evaluated dose analysis; N = number of subjects in analysis set; n = number of subjects classified as seizure-free during the respective period/phase of the last evaluated dose; PP = Per Protocol; QD = once daily.

Note: Data for the Maintenance Period and Extension Phase are presented only up to the cut-off date and are interim in nature.

If the proportion of seizure free subjects at each dose level (i.e. those completing the Evaluation Period at the last evaluated dose) is determined based on the total number of subjects in the PP set for the entire treatment group (i.e. 388 subjects for ESL and 397 subjects for CBZ-CR), the overall proportion was similar in the ESL QD groups (54.1% for 800 mg, 11.1% for 1200 mg and 5.9% for 1600 mg) and in the CBZ-CR BID groups (59.7% for 200 mg, 11.9% for 400 mg, and 4.0% for 600 mg).

Seizure frequencies adjusted for exposure time until the end of the Evaluation, Maintenance and Extension periods were slightly higher in the ESL group than the CBZ-CR group at all dose levels. In the PP set, seizure frequencies until the end of the different periods ranged from 5.21 to 7.18 per 100 patient-years in the ESL group and from 3.18 to 3.94 per 100 patient-years in the CBZ-CR group at dose level A. Results were similar in the FAS.

Seizure occurrence

Overall, the seizure rate during treatment at the last evaluated dose was higher in the ESL group (79/388, 20.4% of subjects) than the CBZ-CR group (57/397, 14.4%), mainly due to more ESL subjects experiencing seizures during the evaluation period (41/357, 11.5% ESL vs. 19/370, 5.1% CBZ-CR subjects). There was no clear trend in the seizure rates of CBZ-CR vs. ESL treated subjects at different dose levels during the titration and stabilization period.

The data were largely in line with the results for treatment failure time at last evaluated dose level.

Quality of Life in Epilepsy Inventory-31

Quality of life in Study 311 was assessed using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31). In the PP set, the mean overall QOLIE-31 scores at baseline were similar in the ESL group (mean of 65.7 points) and the CBZ-CR group (mean of 65.9 points), and comparable improvements were seen in both treatment groups for the overall scores throughout the study. Improvements from baseline in the QOLIE-31 sub-scores for global assessment and T-scores were also similar between the treatment groups. The QOLIE-31 results in the FAS supported the results in the PP set.

- Subgroup analyses

Seizure frequency

The majority of subjects had ≤ 4 seizures in the 3 months prior to baseline: 277/388 (71.4%) of ESL and 293/397 (73.8%) of CBZ-CR subjects. During the last 12 months prior to baseline, the proportions of patients with ≤ 4 seizures were 219/388 (56.4%) in the ESL arm and 297/397 (55.2%) in the CBZ-CR arm.

In the PP set, the proportion of seizure-free subjects during the Evaluation Period was similar between treatment arms for the subgroup with ≤4 seizures in the last 3 months before baseline (ESL: 209/277 [75.5%], CBZ-CR: 226/293 [77.1%]) and the last 12 months (ESL: 167/219 [76.3%], CBZ-CR: 166/219 [75.8%]).

The proportion of seizure-free subjects was higher (>10% difference) in CBZ-CR compared to ESL subjects with > 4 seizures in the last 3 months (ESL: 67/111 [60.4%], CBZ-CR: 74/104 [71.2%]; ARD -10.3%, 95%-CI: -22.54; 1.94) and with > 4 seizures during the last 12 months (ESL: 109/169 [64.5%], CBZ-CR: 134/178 [75.3%]; ARD -8.97%, 95%-CI: -18.39; 0.45) during the Evaluation period; PP set. Similar results were observed in the FAS. Following 1 year of treatment, the CBZ-CR group continued to have a higher proportion of seizure-free subjects in the subgroup with >4 seizures in the last 3 months (>5% difference) and last 12 months (>10% difference) before baseline.

No interaction between treatment and seizure frequency at baseline was observed during the Evaluation Period based on the logistic regression with region and baseline seizure frequency as factors; there was also no interaction between treatment and seizure frequency at baseline during 1 year of treatment.

Baseline seizure type (worst seizure type)

The majority of subjects had partial seizures evolving to secondarily generalised seizures at baseline and the proportions were comparable between treatment groups (ESL: 249/388 [64.2%], CBZ-CR: 239/397 [60.2%]). The subgroups of subjects with simple partial seizures (ESL: 95/388 [24.5%], CBZ-CR: 105/397 [26.5%]) and complex partial seizures (ESL: 44/388 [11.3%], CBZ-CR: 53/397 [13.4%]) at baseline were relatively small.

A similar proportion of subjects with partial seizures evolving to secondarily generalised seizures at baseline were seizure-free during the Evaluation Period (ESL: 185/249 [74.3%], CBZ-CR: 184/239 [77.0%]; ARD -2.66%, 95%-CI: -9.98; 4.66). Fewer subjects with complex partial seizures at baseline were seizure-free during the Evaluation Period in the ESL group (61/95 [64.2%]) than in the CBZ-CR group (78/105 [74.3%]; ARD -11.53%, 95%-CI: -23.39; 0.33), while for the subgroup with simple partial seizures at baseline, the proportion of seizure-free subjects during the Evaluation Period was similar between groups (ESL: 30/44 [68.2%], CBZ-CR: 38/53 [71.7%]).

During 1 year of treatment, the ARD to be seizure-free was generally consistent with the results observed during the Evaluation Period.

No interaction between treatment and seizure type at baseline was observed during the Evaluation Period based on the logistic regression with region and baseline seizure type as factors (for the PP set, or the FAS). There was also no interaction between treatment and seizure type during 1 year of treatment.

Age

More than 90% of subjects in both treatment groups were <65 years old. The proportion of seizure-free subjects <65 years during the Evaluation Period were 260/362 [71.8%] ESL subjects and 280/366 [76.5%] CBZ-CR subjects (ARD -4.35%, 95%-CI: -10.53; 1.82). The proportion of seizure-free subjects aged ≥65 years were 16/26 [61.5%] ESL subjects and 20/31 [64.5%] CBZ-CR subjects (ARD -9.27%, 95%-CI: -34.62; 16.08).

During 1 year of treatment, the proportion of seizure-free subjects <65 years was 65.5% (237/362 subjects) in the ESL group and 71.9% (263/366 subjects) in the CBZ-CR group, and for subjects ≥65 years the proportion was 53.8% (14/26 subjects) in the ESL group and 51.6% (16/31 subjects) in the CBZ-CR group.

Results in the FAS were similar with respect to Evaluation Period and during 1 year of treatment, respectively.

No interaction during the Evaluation Period between treatment and age group was observed based on the logistic regression with region and age group as factors (PP and FAS set). There continued to be no interaction between treatment and age group during 1 year of treatment (PP and FAS set).

Previous AED use (a single AED for a maximum of 2 weeks)

In the PP set, a subgroup of approx. 15% subjects in both treatment groups was previously treated with an AED. Overall, in the PP set during the Evaluation Period, the percentage of seizure-free subjects not previously treated with AEDs was similar in the ESL group (239/328 subjects [72.9%]) and the CBZ-CR group (251/340 subjects [73.8%]). A smaller proportion of subjects previously treated with AEDs were seizure-free in the ESL group (37/60 subjects [61.7%]) compared to the CBZ-CR group (49/57 subjects [86.0%]; ARD -22.2%, 95%-CI: -37.12; -7.28).

During 1 year of treatment, the results were consistent with those seen during the Evaluation Period.

The logistic regression with region and previous treatment with AEDs as factors confirmed an interaction between previous AED use and treatment during the Evaluation Period in the PP set (p=0.0125). The results in the FAS were similar. An interaction was also seen between previous AED use and treatment during 1 year of treatment (PP set: p=0.0047, FAS: p=0.0080).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 – Summary of efficacy of study 311

Title: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomised, active-controlled, parallel-group, multicentre clinical study		
Study identifier	BIA-2093-311	
Design	Multicentre, double-blind, randomized, parallel-group, active-controlled	
	Duration of main phase:	Evaluation phase: 26 weeks Maintenance phase: 26 weeks
	Duration of Run-in phase:	Screening phase: 1 week Titration period: 1 week, Stabilisation period: 1 week
	Duration of Extension phase:	Evaluation study day 366 until final endpoint visit (up to 300 weeks)
Hypothesis	Non-inferiority	

Treatments groups	ESL		Eslicarbazepine acetate as tablets at 3 dose levels: 800mg/day, 1200mg/day or 1600 mg/day; 401 patients randomised; 52 weeks
	CBZ-CR		Carbamazepine (controlled release) tablets at 3 dose levels: 400mg/day, 800 mg/day or 1200mg/day; 412 patients; randomised; 52 weeks
Endpoints and definitions	Primary endpoint	% seizure freedom 6 months	Proportion of subjects who were seizure free for the entire 26-week evaluation period (for PP population)
	Secondary endpoint	% seizure free 1 year	Proportion of seizure-free subjects during 1 year of treatment at the last evaluated dose (for FAS and PP population).
	Secondary endpoint	Time to first seizure	Time to first seizure at the last evaluated dose (treatment failure time) at the end of the evaluation period (Day 182)
Database lock	24 September 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis was conducted on the Per Protocol (PP) set included all subject from the Full Analysis Set (FAS: all subjects randomised and treated with at least 1 dose of study drug after randomisation.) but excluding subjects with major protocol deviations. 26 weeks or 1 year (52 weeks)		
Descriptive statistics and estimate variability	**Treatment group**	**ESL**	**CBZ-CR**
	Number of subjects (PP set)	**388**	**397**
	Seizure freedom 6 months, n (%)	276 (71.1)	300 (75.6)
	Seizure freedom 1 year, n (%)	251 (64.7)	279 (70.3)
	Time to first seizure, Kaplan-Meier estimate	0.12	0.06
	25% Quartile of time to first seizure, days	572	1217
	95% CI (25% Quartile)	410; 843	891; NE

Effect estimate per comparison	Primary endpoint: Seizure freedom 6 months	Comparison groups	ESL vs CBZ-CR
		Average Risk Difference (ARD)	-4.28%
		95% CI	-10.30; 1.74
	Secondary endpoint: seizure freedom during 1 year	Comparison groups	ESL vs CBZ-CR
		ARD	-5.46%
		95% CI	-11.88; 0.97
	Secondary endpoint: Time to first seizure	Comparison groups	ESL vs CBZ-CR
		Hazard Ratio	1.87
		95% CI	1.35; 2.61
Notes	Non-inferiority was concluded when the lower limit of the two-sided 95% CI was greater than or equal to -12% absolute difference. Results for the analyses of seizure freedom rates at 6 months and 1 year on the FAS were consistent with the analyses with the PP set.		

Analysis description	Subgroup Analyses		
Analysis population and time point description	The primary analysis at 26 weeks was repeated on the PP set for a number subgroups including: - baseline seizure frequency: > 4 seizures last year) - baseline (worst) seizure type: secondary generalized, complex partial) - age group: ≥ 65 years) - previous AED use		
Descriptive statistics and estimate variability	**Treatment group**	**ESL**	**CBZ-CR**
	Number of subjects with >4 seizures during the year prior to baseline (%)	**169**	**178**
	% seizure-free during 6 months	64.5%	75.3%
	Number of subjects with complex partial seizures at baseline	**95**	**105**
	% seizure-free during 6 months	64.2%	74.3%
	Number of subjects with secondarily generalised seizures at baseline	**249**	**239**
	% seizure-free during 6 months	74.3%	77.0%
	Number of subjects ≥ 65 years	**26**	**31**
	% seizure-free during 6 months	61.5%	64.5%
	Number of subjects with previous AED use	**60**	**57**
	% seizure-free during 6 months	61.7%	86.0%
Effect estimate per comparison	Subgroup: **> 4 seizures within 1 year prior to baseline**	Comparison groups	ESL vs. CBZ-CR
		ARD	-8.97%
		95% CI	-18.39; 0.45
	Subgroup: **Complex partial seizures at baseline**	Comparison groups	ESL vs. CBZ-CR
		ARD	-11.53
		95% CI	-23.39, 0.33
	Subgroup: **Secondarily generalised seizures at baseline**	Comparison groups	ESL vs. CBZ-CR
		ARD	-2.66
		95% CI	-9.98, 4.66
	Subgroup: **≥ 65 years**	Comparison groups	ESL vs. CBZ-CR
		ARD	-9.27
		95% CI	-34.62, 16.08
	Subgroup: **Previous AED use**	Comparison groups	ESL vs. CBZ-CR
		ARD	-22.20
		95% CI	-37.12, -7.28

Supportive study(ies)

Studies 039-045 and 039-046

Two identically designed conversion-to-monotherapy studies (studies 039-045 and 039-46) have been performed between Apr 2009 and May 2013 (study 045) and Jun 2010 and Nov 2012 (study 046), respectively. Both studies were primarily intended to support the approval of ESL monotherapy in the US.

The studies were double-blind, randomised, historical control, multicentre studies in male and female subjects (aged 16 to 70 years, inclusive) with POS. The results were provided as supportive data in this application.

The studies had an 8-week baseline period followed by 18 week treatment period consisting of a 2 weeks titration period, 6 week tapering period of concomitant AED(s) and a 10 week ESL monotherapy period.

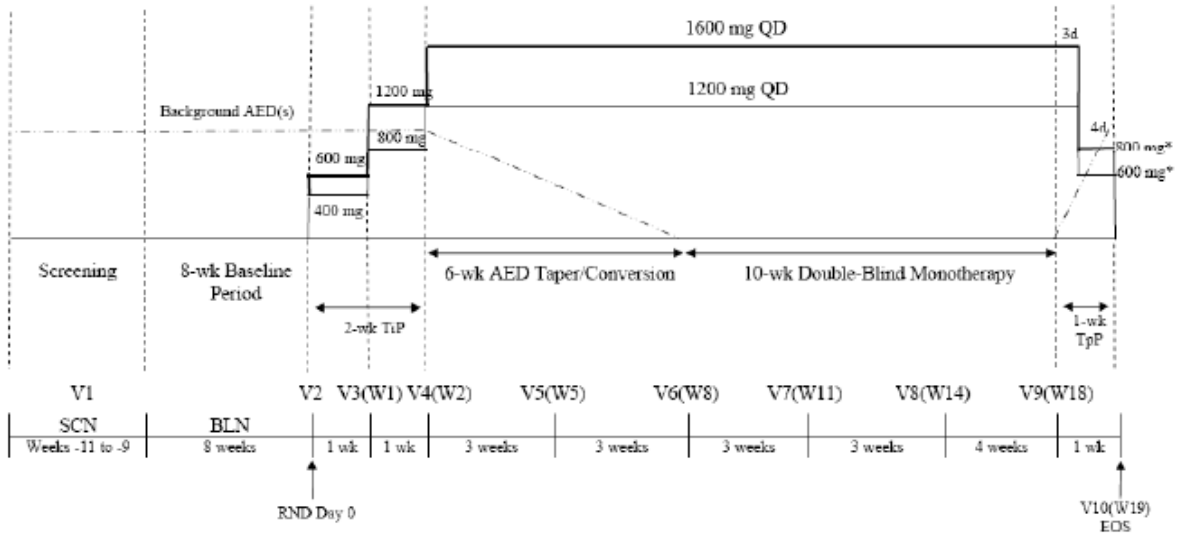


Figure 6 – Overview of the Design of Studies 045 and 046

Subjects were randomised in a 2:1 ratio into the treatment arms: ESL 1600 mg QD or ESL 1200 mg QD.

The main inclusion criteria were:

- Male and female patients between the ages of 16 to 70 years (inclusive) with a medical diagnosis of partial epilepsy defined by the Classification of Seizures of the ILAE as partial onset seizures.
- At least 4 seizures during the 8-week baseline period with no 28-day seizure-free period.
- Stable treatment with 1-2 AEDs during the last 4 week prior to screening

The **primary efficacy endpoint** for each subject was study exit by meeting at least one of the prospective five exit criteria:

1. One episode of status epilepticus.

2. One secondarily generalized partial seizure (in subjects who did not have generalized seizures during six months prior to screening).

3. A two-fold increase in any consecutive 28-day seizure rate compared to the highest consecutive 28-day seizure rate during the 8-week baseline period.

4: A two-fold increase in any consecutive 2-day seizure rate compared to the highest consecutive 2-day seizure rate during the 8-week baseline period.

5: Worsening of seizures or increase in seizure frequency considered serious or requiring intervention.

The cumulative exit rate for a treatment arm was defined as the proportion of subjects meeting at least one of these exit criteria over a 16-week study period.

The **key secondary endpoint** was the proportion (%) of seizure-free subjects during the 10-week double-blind monotherapy period.

Other secondary endpoints included change in seizure frequency from baseline and 50% responder rate.

The efficacy analyses were based on the efficacy (EFF) population, i.e. all subjects in the Intent-To-Treat (ITT) population who had entered the AED taper/ESL conversion period.

The primary comparison was against a historical control, based upon combined exit rates from 8 different monotherapy studies that used pseudo-placebos (French et al., 2010).

The cumulative exit rate was estimated based on Kaplan-Meier methodology. Subjects were censored at the time they prematurely withdrew from the study for any reason other than the exit criteria or at 112 days for subjects who have not met any of the exit criteria. The primary comparison was the 1600 mg treatment arm against the historical control, whereby the lower bound of a prediction interval (computed assuming an 80% exit rate for the pseudo-placebo treatment and a sample size of 50 subjects) was set as a hypothesis testing criterion ("threshold") for the determination of efficacy. The lower bound of the 80% prediction interval (PI) for two independent studies was 72.2%, and the lower bound of the 95% prediction interval for a single study was 65.3%. If the upper end of the 95% CI of 1600 mg QD arm fell below the 72.2% threshold in two independent studies or below the 65.3% threshold in a single study, the null hypothesis that the exit rate in the 1600 mg QD arm equals the combined exit rate observed in the historical control studies was rejected. If the primary null hypothesis of the 1600 mg group versus historical control was rejected, efficacy of the 1200 mg treatment arm versus historical control was evaluated in the same manner.

Number of subjects analysed:

- Study 045: 193 randomised (128 ESL 1600 mg, 65 ESL 1200 mg), EFF set: 178 subjects, PP set: 139 subjects.
- Study 046: 172 randomised (114 ESL 1600 mg, 58 ESL 1200 mg), EFF set: 154 subjects, PP set: 129 subjects.

Demographics were generally similar in the different dose groups. In regard to age, only few subjects >65y of age were included: 1 subject received 1200 mg and 4 subjects received 1600 mg in study 093-045 and no subject >65y of age was included in study 093-046. Baseline medical conditions were similar between dose groups. No concomitant medical conditions have been recorded in these studies.

Main results for study 045:

The Kaplan Meier (KM) estimate of the cumulative 112-day exit rate was 28.7% (95% CI: 21.2%, 38.1%) for the 1600 mg ESL dose group and 44.4% (95% CI: 32.5%, 58.3%) for the 1200 mg ESL dose group.

The upper 95% CI limit of the KM estimate of cumulative 112-day exit rate for the 1600 mg ESL dose group (38.1%) was below the lower limit of the 95% prediction interval for the historical control (65.3%). Subjects treated with 1600 mg QD ESL as monotherapy exited the study at significantly lower rate due to seizure-related events compared to the historical control.

Similar results for the 1200 mg ESL dose group (KM-estimated upper limit of the 95% CI was 58.3% and was lower than the lower limit of the 95% prediction interval for the historical control [65.3%]). Subjects treated with 1200 mg QD ESL as monotherapy exited the study at a significantly lower rate due to seizure-related events compared to the historical control.

There was no statistically significant difference in KM-estimates of the cumulative 112-day exit rate between ESL dose groups (adjusted *P*-value = 0.0739).

Seizure-free rates during the entire 10-week monotherapy period were 7.6% (1600 mg ESL) and 8.3 % (1200 mg ESL). The median % relative decrease in standardised seizure frequency over the double-blind period compared to baseline was 41.5% in the 1600 mg ESL group and 30.9% in the 1200 mg ESL group. The 50% responder rates over the 18-week double-blind period were 39.8% (95% CI: 30.9%, 49.3%) for the 1600 mg ESL dose group and 36.7% (95% CI: 24.6%, 50.1%) for the 1200 mg ESL dose group.

Main results for study 046:

The KM-estimate of the cumulative 112-day exit rate was 12.8% (95% CI: 7.5%, 21.5%) for the 1600 mg ESL dose group and 15.6% (95% CI: 8.1%, 28.7%) for the 1200 mg ESL dose group. The upper 95% CI limit of the KM-estimate of the cumulative 112-day exit rate for the 1600 mg ESL dose group (21.5%) was below the lower limit of the 95% prediction interval for the historical control (65.3%). Subjects treated with 1600 mg QD ESL as monotherapy exited the study at significantly lower rate due to seizure-related events compared to the historical control.

Similar results were obtained for the 1200 mg ESL dose group (KM-estimated upper limit of the 95% CI was 28.7% and was lower than the lower limit of the 95% prediction interval for the historical control [65.3%]). There was no statistically significant difference in KM-estimates of the cumulative 112-day exit rate between ESL dose groups (P = 0.6330).

Seizure-free rates during the entire 10-week monotherapy period were 10.0% (1600 mg ESL) and 7.4 % (1200 mg ESL) and during the last four weeks of monotherapy 17.0% (1600 mg ESL) and 16.7% (1200 mg ESL). The median % relative decrease in standardised seizure frequency over the double-blind period compared to baseline was 47.5% in the 1600 mg ESL group and 36.1% in the 1200 mg ESL group. Neither treatment nor baseline seizure frequency were significant predictors of relative change in seizure frequency. The 50% responder rates over the 18-week double-blind period were 46.0% (95% CI: 36.0%, 56.3%) for the 1600 mg ESL dose group and 35.2% (95% CI: 22.7%, 49.4%) for the 1200 mg ESL dose group.

2.4.3. Discussion on clinical efficacy

To support the broadening of the indication of Zebinix to include POS monotherapy in adult epilepsy patients, the MAH submitted the results of one Phase 3 study conducted in adults (≥ 18 years) with newly diagnosed epilepsy experiencing POS (study 311). Supportive data were presented from 2 conversion-to-monotherapy trials. No dose-response studies were conducted.

Design and conduct of clinical studies

The primary objective of study 311 was to demonstrate that monotherapy with ESL was non-inferior to monotherapy with controlled-release CBZ in adults (≥ 18 years) with newly diagnosed epilepsy experiencing POS. In- and exclusion criteria for this study were generally adequate in order to identify a study population in line with the proposed target population of the claimed monotherapy indication. At the time of the cut-off for the study report (24 Sep 2015), the Maintenance Period was still ongoing and had been completed by 240 (59.9%) ESL subjects and 264 (61.1%) CBZ-CR subjects.

The study was designed with stepwise fixed dose increments based on individual response at 3 different dose levels, i.e. dose level A (ESL 800 mg QD, CBZ-CR 200 mg BID), level B (ESL 1200 mg QD or CBZ-CR 400 mg BID) and level C (ESL 1600 mg QD or CBZ-CR 600 mg BID). Whereas ESL dose levels A and B in study 311 were within the dose range currently approved for ESL adjunctive treatment of adults with POS, the highest dose level, 1600 mg ESL QD, exceeded the maximum approved dose for add-on therapy (1200 mg QD). See further discussion on dose recommendations below.

The choice of CBZ-CR as the active comparator was agreed. CBZ is widely used as first choice treatment for POS and the controlled-release formulation allows more stable plasma levels of the drug, avoiding peaks in plasma concentration and resulting in an overall better tolerability. Thus, it can be regarded as the active comparator of choice. Furthermore, the chosen dose levels of CBZ-CR were within the approved dose range of CBZ, in accordance with the most commonly used doses in clinical practice and in line with published literature, which suggests that the majority of subjects with newly diagnosed epilepsy respond to their first AED at a low dose (e.g. Brodie et al. 2007).

The primary efficacy endpoint was the proportion of subjects who were seizure free for the entire 26-week

evaluation period at the last evaluated dose level. Subjects who dropped out during this 26-week period were considered as non-seizure-free in the primary efficacy analysis. Seizure freedom rates were also evaluated after 1 year of treatment at the last evaluated dose level (secondary endpoint). Non-inferiority (NI) of ESL to CBZ-CR was considered demonstrated if the one-sided 97.5% CI for the absolute difference in proportions did not exceed the pre-specified NI margin of -12%. The NI margin had been tightened from a previously proposed -15%. This was further to a CHMP scientific advice in 2009, which perceived an absolute NI margin of -15% as rather large, especially in case of a 26-week seizure freedom rate of 60% used for the sample size calculations. The -12% NI margin was determined assuming a relative difference to CBZ-CR of 20% or less as acceptable. This was based on ILAE guidance considering a relative treatment difference of more than 20% in active controlled monotherapy studies as clinically important (ILAE, 1998; Glauser et al., 2006; Glauser et al., 2013).

Other secondary efficacy variables included time to first seizure at the last evaluated dose, time to withdrawal due to AE or lack of efficacy, time to withdrawal for any reason as well as seizure type and duration of first seizure during the evaluation period.

While the primary analyses were conducted on the PP set, the CHMP considered analyses based on PP and FAS to be of equal importance for analysis of NI, which means that co-primary testing would have been more adequate than sequential testing. However, since both analyses yielded consistent results (see below), the issue was not pursued. Furthermore, the CHMP noted that patients who discontinued treatment were analysed as non-seizure free. Although drop-out and treatment failure may not be independent, considering any drop-out as being non-seizure free probably led to a substantial overestimation of the proportion of patients experiencing a seizure during the evaluation period. In fact, the majority of treatment failures were not due to seizures but due to study discontinuation for other reasons. Thus, the primary endpoint as analysed can be considered as a combined endpoint 'being seizure free + completing the evaluation period at the last dose level', which could indeed be a valid definition of treatment success, in particular as it does not assume continued benefit after treatment discontinuation. However, this endpoint tends to be less sensitive to show differences between active treatments and may lead to an anti-conservative NI comparison. Nevertheless, the secondary Kaplan-Meier analysis of treatment failures provides the proportion of seizure-free patients over time and makes the alternative assumption that the seizure risk of dropouts would have been the same as the seizure risk of patients continuing treatment, which may be more sensitive to show differences between study arms. Furthermore, in response to a request by the CHMP, the MAH providing additional sensitivity analyses employing different assumptions for seizure probability in drop-outs (see discussion on the results below).

Finally, the CHMP questioned a change to the protocol, i.e. deleting 'poor compliance for completion of the eDiary' from the criteria for the PP population, given that the seizure counting in the study depended on the information reported by the study subjects in the diary. The MAH clarified that the total number of subjects considered for 'poor compliance' (< 80%), was a small proportion of the whole population, with 50 (12.9%) subjects in the ESL group and 64 (16.1%) in the CBZ-CR group, and that the poor compliance was partly due to technical problems together with the fact that the eDiaries did not allow for retrospective completion. Furthermore, in a sensitivity analysis, in which subjects with poor diary compliance were removed from the PP subset, the actual responder rates were very similar compared to the original analysis. Based on this information, the CHMP was reassured that the cases of poor diary compliance did not affect the overall study outcome.

Overall, the study design including the choice of endpoints and statistical analyses were considered acceptable by the CHMP and in line with the recommendations of the CHMP Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98Rev.2/Corr). Furthermore, study conduct and baseline data were considered acceptable.

Of the 815 subjects randomised in the study (401 subjects to ESL and 414 to CBZ-CR) more than 70%

completed the evaluation period. Notably, the percentage of discontinuations due to lack of efficacy was slightly higher in the ESL group compared to the CBZ-CR group (7% vs. 2.9%), however, the opposite was seen regarding AEs, although with an even smaller difference (8.2% vs. 10.7%).

The distribution of subjects across dose levels was generally similar. However, there were somewhat higher percentages of ESL subjects that needed up-titration to dose level B or C, respectively, compared to CBZ-CR. The majority of subjects remained at dose level A (ESL: 271/401 [67.6%], CBZ-CR: 317/412 [76.9%]). As a consequence, the number of subjects at dose level B (ESL: 70/401 [17.5%], CBZ-CR: 61/412 [14.8%]) and C (ESL: 60/401 subjects [15.0%], CBZ-CR: 34/412 [8.3%]) as last evaluated dose was limited. There was also higher percentage of ESL subjects using concomitant AEDs (25.7%) compared to CBZ-CR subjects (18.0%) during the evaluation and down-titration periods. To understand a possible impact of this imbalance on the study outcome, a sensitivity analysis was conducted in which patients with concomitant AEDs were regarded non-responders. The sensitivity analysis yielded similar results as the original analysis, which was reassuring.

Demographic data and baseline disease characteristics were generally balanced across treatment groups. In the PP set, in both treatment groups a median of 4 seizures was experienced within 1 year prior to enrolment and a median of 2 seizures was experienced within 3 months prior to enrolment.

Efficacy data and additional analyses

For the primary efficacy endpoint, the proportion of seizure free subjects during the 26 week evaluation period at the last evaluated dose level was slightly lower in the ESL arm compared to the CBZ-CR group (276/388 [71.1%] versus 300/397 [75.6%], PP set). The average risk difference (ARD) was -4.28 (95% CI: -10.3; 1.74) and non-inferiority of ESL with CBZ-CR was concluded based on the pre-specified non-inferiority margin of an absolute difference of -12%, as the one-sided 97.5% CI was greater than -12%. The results from the analysis on the FAS as well as from the planned sensitivity analyses were largely consistent with the primary analysis, thus showing that the conclusion of non-inferiority did not depend on the method chosen for the primary analysis. This included tipping point analyses with alternative assumptions on seizure probability in drop-outs to alleviate concerns that the primary analysis considering drop-outs as non-seizure free could have diluted the difference between treatment arms. Particularly, when assuming up to 3 times larger seizure rates in CBZ-CR drop-outs compared to CBZ-CR completers, NI still holds at assumed seizure rates for the ESL group 2.5 time higher than for CBZ-CR, thus showing that NI did not critically depend on the drop-out seizure frequency.

Consistent results were also shown for the analyses of seizure-free subjects after 1 year of treatment (251/388 [64.7%] versus 279/397 [70.3%] seizure-free patients in the ESL and in the CBZ-CR group, respectively; ARD: -5.46%, 95% CI: -11.88; 0.97) as well as for the relative risk difference during the evaluation period and during 1 year of treatment.

Notably, across the different analyses for seizure freedom, the lower bound of the 95% CI was consistently close to the -12% margin, in particular when considering 1 year of treatment. For the latter, the lower bound of the 95% CI was slightly below -12% when analysed using the Farrington-Manning method in the PP population and slightly above for all the other analyses. However, the NI margin of -12% was based on the assumption of a 60% seizure freedom rate in the CBZ-CR arm.

Despite the fact that non-inferiority was robustly demonstrated from a statistical point of view, the majority of efficacy analyses show a numerically smaller effect size for ESL compared to CBZ-CR. The probability for treatment failure at the end of the evaluation period, i.e. the risk of a seizure at the last evaluated dose based on time to event analysis (Kaplan-Meier analysis and Cox regression), was twice as high for patients receiving ESL compared to CBZ-CR subjects (12% versus 6%). This finding was seen both overall and when limiting the analyses to subjects on dose level A as last evaluated dose. In fact, statistically significant superiority of CBZ-CR versus ESL was observed (p=0.0002 for the global KM analysis). At the same time,

the actual probability to be seizure free after 26-weeks of treatment resulting from the Kaplan Meier analysis was high with 88% of ESL and in 94% of CBZ-CR subjects with an upper bound of 95% CI of 10.5%. Whereas these findings relate to a relatively low risk level of seizures, the CHMP noted that the intended patient population of newly diagnosed adults with POS has a comparably high probability to become seizure free with effective anti-convulsant therapy, the latter constituting the general treatment aim in these patients. Against this background, doubling of the risk of seizure and an absolute difference of 6% cannot be ignored. Altogether, the CHMP concluded that the available evidence point towards a slightly lower efficacy of ESL compared to CBZ-CR.

The CHMP furthermore noted the very low incidence of seizures during the 26-week observation period, which could be consistent not only with highly effective treatments in the two study arms, but also with a patient population at an inherently low risk of seizures. The proportions of patients for whom no seizures were actually observed were substantially larger than the point estimate of the primary efficacy analysis (Kaplan-Meier estimates of 94% and 88% for CBZ-CR and ESL, respectively). Nevertheless, actual 6-months seizure freedom rates around 90% in monotherapy studies are not completely unusual. Furthermore, at the end of maintenance period (after 1 year of treatment) the proportions of seizure free patients resulting from the Kaplan-Meier analysis (89% and 81%, respectively) were lower than at Month 6, indicating a general risk of seizures for subjects after a longer observation period. The MAH also argued that a newly diagnosed, newly treated population includes, as a principle, a subset of patients with an inherently low risk of seizures and that a frequent finding in monotherapy studies is that newly diagnosed epilepsy patients respond to their first AED already at a low dose. Based on relevant scientific literature (Hauser et al., 1998; Kim et al., 2006; Marson et al., 2008), subjects in study 311, who had a median baseline seizure frequency of 4 seizures during the past 1 year prior to enrolment, were considered at risk for recurrence within 12 months. According to Hauser et al., subjects with two single unprovoked seizures have a risk of recurrence of a third seizure of 76%, with a median time to recurrence of 4.5 months. The CHMP agreed that the high proportion of seizure-freedom in both treatment arms of study 311 was likely not attributable to a patient population of particularly low risk of seizures. Assay sensitivity was consequently regarded sufficient.

Similar to the primary analysis, seizure frequencies adjusted for exposure time until the end of the Evaluation, Maintenance and Extension periods were higher in the ESL group than the CBZ-CR group at all dose levels. In the PP set, seizure frequencies until the end of the different periods ranged from 5.21 to 7.18 per 100 patient-years in the ESL group and from 3.18 to 3.94 per 100 patient-years in the CBZ-CR group at dose level A.

Furthermore, during the evaluation period there was a trend towards more severe seizure types across the 3 dose levels in the ESL group compared to CBZ-CR subjects: 32% (ESL) and 19% (CBZ-CR) of seizures were secondary generalised, 43% (ESL) and 26% (CBZ-CR) were complex partial and 23% (ESL) and 40% (CBZ-CR) were simple partial seizures. At the same time, subgroup analyses by seizure type at baseline revealed similar rates of seizure-freedom in subjects with secondary generalised seizures as worst seizure type at baseline (ESL: 74.3% and CBZ-CR: 77%, respectively). In response to a CHMP request, the MAH presented a subgroup analysis by most frequent seizure type at baseline. In subjects with secondary generalised seizures as the most frequent baseline seizure type, which represented the largest of the respective 3 subgroups of POS, seizure freedom rate was very similar among both treatment arms (ESL: 145/192 [75.5%] versus CBZ: 143/191 [74.9%], ARD 0.16% and 95%CI: -8.14; 8.46). The CHMP considered this analysis to be indicative that ESL monotherapy is also effective in prevention of secondary generalised seizures. No substantial differences between ESL and CBZ-CR treated subjects could be concluded with respect to seizure duration.

The presented subgroup analyses on the primary efficacy variable also seemed to be suggestive of a slightly lower efficacy of ESL in subjects with more severe epilepsy in terms of seizure burden, i.e. subjects with a seizure frequency of > 4 seizures in the last 3 months prior to baseline (ESL: 67/111 [60.4%], CBZ-CR: 74/104 [71.2%]; ARD -10.3%, 95%-CI: -22.54; 1.94) as well as in those with > 4 seizures for the past

12 months (ESL: 109/169 [64.5%], CBZ-CR: 134/178 [75.3%]; ARD -8.97%, 95%-CI: -18.39; 0.45). Similar results were obtained in subjects previously treated with an AED up to 2 weeks (ESL: 37/60 [61.7%]), CBZ-CR: 49/57 [86.0%]; ARD -22.2%, 95%-CI: -37.12; -7.28). While for all these subgroups, lower proportions of seizure-free subjects in the ELS group compared to the CBZ-CR group were seen, at the same time, no interaction between treatment and seizure frequency during 1 year of treatment was found. However, interaction tests have a low power and non-significant interaction does not provide reliable evidence for absence of such interaction. The CHMP acknowledged, that the subgroup of patients with > 4 seizures within 3 months prior to baseline (consisting of < 30% of study subjects) as well as the subgroup with previous AED use (approximately 15% of study subjects) were small and therefore results should be interpreted with caution. Furthermore previous short term AED use can only be regarded as rather vaguely indicative of disease severity.

There were no apparent differences with regards to efficacy in older subjects (≥65 years) compared to younger subjects (< 65 years). The proportion of seizure-free patients aged ≥65 years was very similar in patients receiving ESL compared to CBZ-CR during the evaluation period (16/26 [61.5%] ESL subjects and 20/31 [64.5%] CBZ-CR subjects) and the combined evaluation and maintenance period (14/26 [53.8%] ESL subjects and 16/31 [51.6%] CBZ-CR subjects).

The results after 1 year of treatment could be regarded as indicative of maintenance of the effect of ESL. However, by the cut-off date of the study report, the maintenance phase had only been completed by 59.9% of subjects in the ESL group and 64.1% in the CBZ-CR group. Further, the probability to withdraw from the study at any dose level due to AEs or lack of effect (treatment retention time) was similar between ESL and CBZ-CR groups up to Day 240 (8 months), but increased thereafter in the ESL group to a larger extent than for CBZ-CR. Likewise, the percentage of discontinuations from the study due to any reason was similar for both treatment groups during the initial phase of the study (first 3 months of treatment) and increased afterwards in the ESL more than in the CBZ-CR group. In an effort to justify maintenance of efficacy, the MAH clarified that in fact at the cut-off date of the study report only 6 patients (3 in each arm) had been ongoing in the maintenance phase. Also, the most frequent reason for drop outs during the maintenance period in both treatment groups was lack of efficacy (5.2% of ESL and 3.9% of CBZ-CR subjects), whereas AEs accounted for 0.7% and 1.5% of discontinuations of ESL and CBZ-CR subjects, respectively. The MAH also provided an analysis of seizure-freedom during the maintenance period for subjects on a stable dose for at least 1 year in which subjects with insufficient treatment time were considered non-seizure free, resulting in a similar ARD of ESL compared to CBZ-CR of -5.09 compared to the primary analysis with a lower limit of the 95%% CI of -11.76. Overall, the findings for the maintenance phase were essentially in line with the observations during the evaluation phase. Therefore, maintenance of effect of ESL in POS monotherapy could be regarded as sufficiently justified.

Finally, the CHMP critically reviewed the added value of the new maximum daily dose of 1600 mg ESL given that the design of study 311 did not allow for assessment of dose-response relationship. Furthermore, most patients in the ESL group remained at the lowest possible dose level A (800 mg QD, 271/401) and only 15% (60/401) required up-titration to the maximum allowed dose of 1600 mg ESL QD (level C). However, the finding of a retention rate at dose level C of 43.4% ESL subjects during the evaluation period and 69.6% ESL subjects during the maintenance period, indicates that a relevant subset of the subjects who were not seizure free at 1200 mg ESL did profit from a further increase of the ESL dose up to 1600 mg/day. Therefore, the CHMP was of the view that a maximum dose of 1600 mg/day could be recommended provided that safety and tolerability are also acceptable (see section 2.5.). However, as only few elderly patients were recruited into the study (less than 8% of the study population) and since amongst these, only one single patient received ESL at the maximum dose of 1600 mg/day, the CHMP was of the view that the new proposed maximum dose could not be recommended for this population.

2.4.4. Conclusions on the clinical efficacy

Whereas the pivotal clinical study concluded on non-inferiority of ESL compared to CBZ-CR based on the pre-specified non-inferiority margin of -12%, the risk of seizure at the last evaluated dose doubled from 6% in the CBZ-CR group to 12% in the ESL group and throughout the efficacy analyses a consistent trend towards a slightly lower efficacy of ESL compared to CBZ-CR was observed, in particular with regard to more severe epilepsy. However, in the context of a population at risk of recurring seizures, the resulting Kaplan Meier seizures freedom estimates of more than 80% during 1 year of treatment clearly indicate efficacy of ESL. Overall, the CHMP considered that the available clinical efficacy data were adequate to support the present application for an extension of indication of Zebinix to monotherapy of adult epilepsy patients with POS with or without secondary generalisation at doses up to 1600 mg/day.

2.5. Clinical safety

Introduction

At the time of this application, ESL was approved in the EU for use as adjunctive therapy in adults with POS with or without secondary generalisation. The known safety profile of ESL was largely based on the data from placebo-controlled Phase 2 and Phase 3 clinical trials with ESL as adjunctive therapy in adult epileptic subjects supporting the initial marketing authorisation application (Studies BIA-2093-201, -301, -302, and -303 [hereafter referred to as studies 201, 301, 302, and 303]). A subsequent Phase 3 study BIA-2093-304 (study 304) supplemented the original safety database.

In these studies, a dose-dependent increase in treatment-emergent adverse events (TEAEs) was observed for several Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs), including possibly related TEAEs and TEAEs leading to discontinuation of study medication. As per the original marketing authorisation application for Zebinix, TEAEs leading to discontinuation were reported in 8.7%, 11.6%, and 19.3% of the patients receiving 400 mg, 800 mg, and 1200 mg ESL, respectively, based on an integrated safety data analysis. In the subsequent study 304 (Part 1) discontinuations due to TEAEs were reported for 12% and 25.7% of subjects with doses of 800 mg and 1200 mg ESL.

The most common TEAEs in the placebo-controlled trials in adult epileptic subjects were *dizziness, somnolence (very common, i.e. in ≥1/10 patients), headache and nausea (common, i.e. in ≥1/100 to <1/10 patients)*. There were no changes in laboratory parameters that indicated a safety concern and there were also no clinically relevant changes in vital signs, body weight or body mass index (BMI) during the studies.

Limited data in paediatrics were available from studies BIA-2093-305 and -208. The safety profile observed in children was generally consistent with the profile in adults. In children, the most common side effects were diplopia (double vision, seen in around 5 patients in 100), somnolence (seen in around 8 patients in 100) and vomiting (seen in around 5 patients in 100).

Furthermore, ESL is a third-generation dibenz/b,f/azepine AED and is closely related to oxcarbazepine. Following oral administration of both active substances, the same active moieties, i.e. eslicarbazepine, R-licarbazepine and oxcarbazepine, are found in plasma, though in somewhat different proportions. Therefore, class related adverse reactions which have been reported with oxcarbazepine including rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias, while not observed during the ESL epilepsy clinical development program, cannot be excluded with ESL use.

The safety assessment of the present application for use of ESL as POS monotherapy in adults was mainly based on the results of the (ongoing) pivotal double-blind active-controlled Phase 3 study 311. Pooled safety findings from the 2 conversion-to-monotherapy Phase 3 studies 045 and -046 were provided as supportive data. For an overview of the study design see section 2.4.

Safety was assessed in all three studies by collecting data for AEs, safety laboratory variables, electrocardiogram (ECG) readings, vital signs, physical examinations, and Columbia Suicide Severity Rating Scale (C-SSRS). In addition, study 311 collected data on neurological examinations and Bond-Lader visual analogue scales (BL-VAS). TEAEs were summarised by treatment group and dose. TEAEs were defined as all AEs with onset or worsening after first intake of randomised investigational medicinal product until 4 weeks after last intake of randomised investigational medicinal product. The number and percentage of subjects with a TEAE were tabulated by MedDRA SOC and preferred term (PT).

TEAEs were also summarised by relationship to study drug, and by maximum intensity. The assessment of the relationship/causality of a TEAE to treatment in study 311 was a clinical decision by the investigator based on all available information at the time of the completion of the electronic case report form.

During the course of the procedure, the MAH provided additional data from a long term open label extension study (study 093 050), which enrolled subjects who had completed, discontinued, or exited from studies 093-045 or 046 and completed at least the first 3 weeks of the 18-week double-blind treatment period. The purpose of Study 093 050 was to confirm the long term safety and tolerability of ESL administered in a flexible dose range of 800 mg to 2400 mg once-daily in subjects with POS, with or without secondary generalization. The initial study duration was 1-year with the option of continuing study drug treatment post-1-year until a subject discontinued the study. The cut-off date for this study was 21 March 2014.

Patient exposure

As of the date of data-cut-off for this application (24-Sep-2015), a total of 1178 epileptic adult subjects with POS had been enrolled and treated in the 3 clinical studies supporting this application (311, 045 and 046). Of these, 766 subjects were exposed to at least 1 dose or repeated doses of up to a maximum of 1600 mg/day of oral ESL monotherapy.

- *Pivotal study 311*

The safety set of study 311 included all subjects who received at least 1 dose of investigational medicinal product. These were a total of 401 and 412 patients in the ESL and CBZ-CR group, respectively. All subjects were analysed according to the treatment received. Subjects receiving more than 1 type of investigational medicinal product in error were analysed according to the treatment they received the longest.

The total mean treatment duration was shorter in the ESL group (577.1 days) compared to the CBZ-CR group (614.7 days) since patients in ESL dose level B and C had a shorter total mean treatment duration than the respective CBZ-CR dose levels (dose level B: ESL 494.8 days vs. CBZ-CR 641.3 days; dose level C: ESL 411.9 days vs. CBZ-CR 523.4 days). Treatment duration was similar in the 2 treatment groups at dose level A (ESL 635.0 days, CBZ-CR 619.3 days).

Table 11 – Mean Daily Dose by Last Evaluated Individual Dose – Study 311 (Safety set/FAS)

	ESL				CBZ-CR			
Statistic	800 mg QD (N=271)	1200 mg QD (N=70)	1600 mg QD (N=60)	Total (N=401)	200 mg BID (N=317)	400 mg BID (N=61)	600 mg BID (N=34)	Total (N=412)
n	271	70	60	401	317	61	34	412
Mean	763.8	1165.0	1494.8	943.2	377.7	751.8	1109.8	493.5
SD	82.22	70.73	125.02	289.47	48.15	89.51	117.50	236.06
Min	300	855	1173	300	100	410	738	100
Max	798	1200	1600	1600	399	798	1197	1197

BID = twice daily; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; FAS = Full Analysis Set; Max = maximum; Min = minimum; n = number of subjects with data; N = number of subjects in the analysis set; QD = once daily; SD = standard deviation.

The majority of subjects (271 of 401, 68%) remained on the lowest dose level A (800mg QD ESL). A similar

distribution was observed in the CBZ-CR group. Only 15% of subjects (60 of 401) in study 311 were in the highest dose group C.

- *Supportive study pool (conversion-to-monotherapy studies 045 and 046)*

A total of 365 subjects were exposed to at least 1 dose of ESL (123 patients in the ESL 1200 mg QD and 242 patients in the ESL 1600 mg QD group). The overall median number of days of overall ESL administration (1200 and 1600 mg/d) during the 18-week double-blind period was 126.0 days (range: 1 to 147 days). The overall median of the average daily ESL dose was 1571.4 mg (range: 70 to 1686 mg) over the AED taper/conversion and monotherapy periods. A total of 66 of 242 subjects, who received 1600 mg ESL (27.3%) have been exposed for at least 18 weeks (4.5 months).

- *Long-term open label extension of conversion-to-monotherapy studies 045 and 046 (study 050)*

In study 050 as of the cut-off date, 274 subjects received at least 1 dose of study medication. A total of 65.7% of subjects completed the 1-year period, 8.8% were ongoing in the 1-year period, and 25.5% of subjects discontinued during the 1-year period. Subjects were allowed to increase the ESL dose to a maximum dose of 2400 mg QD and there were 90 subjects who used doses ≥2000 mg (modal dose), and 73 of these were on treatment for at least a year.

The overall median number of days of ESL administration combined across studies was 490.0 days (range: 1 to 1671 days). There was 542.4 subject-years of exposure for ESL-treated subjects overall, of which 195.1 subject-years of exposure was in the highest dose category (ESL ≥ 2000 mg). A total of 257 subjects had a duration of ESL exposure of more than 6 months, 225 subjects had a duration of ESL exposure of more than 1 year, and 134 subjects had a duration of ESL exposure of more than 2 years. For modal daily doses ≥ 1400 mg ESL (representing the 1600 mg, 2000 mg, and 2400 mg doses), there were 212 subjects with ESL exposure of more than 6 months, 190 subjects with ESL exposure of more than 12 months, and 113 subjects had a duration of ESL exposure more than 2 years.

Adverse events

- *Pivotal Study 311*

Similar percentages of subjects experienced at least 1 TEAE in the ESL and CBZ-CR group (75.3% and 77.7%). At dose level A (i.e. the dose level at which the majority of subjects in both groups completed the Evaluation Period), the incidence of TEAEs was comparable between treatment groups (ESL: 76.0%, CBZ-CR: 79.5%) (see Table 12). Overall, TEAEs possibly related to treatment were reported by fewer subjects in the ESL group (41.1%) than in the CBZ-CR group (49.5%), which was also true when comparing ESL and CBZ-CR at dose levels A and C, but the opposite was observed at dose level B (ESL: 52.9%, CBZ-CR: 42.6%).

Both treatment groups had a similar overall incidence of serious TEAEs (ESL: 10.0%, CBZ-CR: 10.9%), whereas more subjects in the ESL dose groups B and C had serious TEAEs compared to the respective CBZ-CR dose groups (12.9% for ESL vs. 6.6% for CBZ-CR in dose group B and 15% for ESL vs. 2.9% for CBZ-CR in dose group C). A similar distribution could be detected for possibly related serious TEAEs. Fewer subjects discontinued treatment due to TEAEs in the ESL group (13.5%) than the CBZ-CR group (18.0%) (see Table 11). Four subjects (2 in each treatment group) experienced TEAEs that were fatal (glioblastoma multiforme and cardiac arrest in the ESL group, suicide and lung adenocarcinoma in the CBZ-CR group).

Table 12 – Summary of TEAEs by last evaluated individual dose – Study 311 (Safety set)

Category of TEAE	Number (%) of subjects							
	ESL				CBZ-CR			
	800 mg QD (N=271)	1200 mg QD (N=70)	1600 mg QD (N=60)	Total (N=401)	200 mg BID (N=317)	400 mg BID (N=61)	600 mg BID (N=34)	Total (N=412)
Any TEAE	206 (76.0)	55 (78.6)	41 (68.3)	302 (75.3)	252 (79.5)	41 (67.2)	27 (79.4)	320 (77.7)
At least possibly related TEAEs	105 (38.7)	37 (52.9)	23 (38.3)	165 (41.1)	156 (49.2)	26 (42.6)	22 (64.7)	204 (49.5)
Any serious TEAE	22 (8.1)	9 (12.9)	9 (15.0)	40 (10.0)	40 (12.6)	4 (6.6)	1 (2.9)	45 (10.9)
At least possibly related serious TEAEs	3 (1.1)	3 (4.3)	2 (3.3)	8 (2.0)	10 (3.2)	1 (1.6)	0 (0.0)	11 (2.7)
TEAEs leading to IMP discontinuation	32 (11.8)	17 (24.3)	5 (8.3)	54 (13.5)	57 (18.0)	12 (19.7)	5 (14.7)	74 (18.0)

BID = twice daily; CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; IMP = investigational medicinal product; N = number of subjects in the analysis set; QD = once daily; TEAE = treatment-emergent adverse events.

TEAEs by SOC and PT

Overall, TEAE incidence rates were lower for ESL compared to CBZ-CR. The pattern of TEAEs was found to be in accordance with the known safety profile of the two drugs (see Table 13).

Most commonly reported TEAEs irrespective of dose levels/groups (>15% of subjects in any treatment group) were reported for the following SOCs: nervous system disorders, infections and infestations, investigations, gastrointestinal disorders, general disorders and administrative site conditions and psychiatric disorders.

The most frequently reported TEAEs (>10% of subjects in any treatment group) were headache (ESL: 22.9%, CBZ-CR: 21.8%) and dizziness (ESL: 13.7%, CBZ-CR: 12.4%; Table 7). At dose levels A and B, headache and dizziness were reported by similar proportions of subjects in either treatment group, while at dose level C, the incidence for both these events was lower in the ESL group (headache: 15.0% ESL versus 23.5% CBZ-CR; dizziness: 16.7% ESL versus 26.5% CBZ-CR).

Relevant differences between groups (defined as a difference of ≥10%) were only found for the TEAE gamma-glutamyltransferase (GGT) increased (4.0% of subjects in the ESL group and 14.6% in the CBZ-CR group). Increased GGT was reported by lower proportions of subjects in the ESL group at all dose levels (ranging from 1.7% at dose level C to 7.1% at dose level B) than the CBZ-CR group (ranging from 11.5% at dose level B to 20.6% at dose level C).

Nasopharyngitis was found at slightly higher incidences in dose groups B and C for ESL compared to CBZ-CR (ESL dose group B and C: 7.1% and 10% versus CBZ-CR dose group B and C: 1.6% and 5.9%).

Hyponatraemia was reported at a slightly higher incidence in subjects on ESL compared to CBZ-CR for each dose group (ESL Dose Group A, B and C: 1.5%, 7.1% and 5% versus CBZ-CR Dose Group A, B and C: 0.9%, 0% and 2.9%).

When comparing TEAEs by last evaluated individual dose (dose groups A, B, and C), a trend was observed towards dose-related increases in the incidences of some of the AEs including abdominal pain, abdominal pain upper, asthenia, fatigue, malaise, fall, aspartate aminotransferase increased, blood creatine phosphokinase increased, memory impairment, tremor, depressed mood, and mood altered. However, in other instances, no trend or even an inverse dose-relationship could be seen.

Table 13 – TEAEs reported in >2% of subjects in either treatment group – Study 311 (Safety set)

Preferred Term	Number (%) of subjects	
	ESL (N=401)	CBZ-CR (N=412)
Any TEAE	302 (75.3)	320 (77.7)
Headache	92 (22.9)	90 (21.8)
Dizziness	55 (13.7)	51 (12.4)
Nasopharyngitis	31 (7.7)	31 (7.5)
Nausea	31 (7.7)	40 (9.7)
Fatigue	28 (7.0)	30 (7.3)
Somnolence	27 (6.7)	34 (8.3)
Back pain	20 (5.0)	18 (4.4)
Hypertension	20 (5.0)	26 (6.3)
Anxiety	18 (4.5)	16 (3.9)
Blood creatine phosphokinase increased	17 (4.2)	16 (3.9)
Diarrhoea	17 (4.2)	17 (4.1)
Influenza	17 (4.2)	22 (5.3)
Vomiting	17 (4.2)	17 (4.1)
Gamma-glutamyltransferase increased	16 (4.0)	60 (14.6)
Abdominal pain upper	15 (3.7)	15 (3.6)
C-reactive protein increased	14 (3.5)	16 (3.9)
Insomnia	13 (3.2)	9 (2.2)
Rash	13 (3.2)	12 (2.9)
Vertigo	13 (3.2)	21 (5.1)
Weight increased	13 (3.2)	17 (4.1)
Hyponatraemia	12 (3.0)	4 (1.0)
Asthenia	10 (2.5)	10 (2.4)
Disturbance in attention	10 (2.5)	6 (1.5)
Hypothyroidism	10 (2.5)	10 (2.4)
Anaemia	9 (2.2)	8 (1.9)
Memory impairment	9 (2.2)	12 (2.9)
Tremor	9 (2.2)	4 (1.0)
Bronchitis	8 (2.0)	12 (2.9)
Contusion	8 (2.0)	3 (0.7)
Cough	8 (2.0)	8 (1.9)
Toothache	8 (2.0)	10 (2.4)
Urinary tract infection	8 (2.0)	10 (2.4)
Viral infection	8 (2.0)	8 (1.9)
Vision blurred	8 (2.0)	7 (1.7)
Alanine aminotransferase increased	7 (1.7)	10 (2.4)
Pyrexia	7 (1.7)	11 (2.7)
Syncope	7 (1.7)	14 (3.4)
Arthralgia	6 (1.5)	11 (2.7)
Aspartate aminotransferase increased	6 (1.5)	9 (2.2)
Abdominal pain	5 (1.2)	11 (2.7)
Fall	5 (1.2)	11 (2.7)
Pain in extremity	5 (1.2)	10 (2.4)
Respiratory tract infection viral	5 (1.2)	9 (2.2)
Dermatitis allergic	2 (0.5)	10 (2.4)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; N = number of subjects in the analysis set; TEAE = treatment-emergent adverse event.

Possibly related TEAEs

Overall incidences of TEAEs (PTs) considered by the investigator to be at least possibly related to treatment were similar between ESL and CBZ-CR (41.1% and 49.5%, see table 8).

Table 14 – TEAEs considered at least possibly related to treatment reported in >2% of subjects in either treatment group – Study 311 (Safety set)

Preferred Term	Number (%) of subjects	
	ESL (N=401)	CBZ-CR (N=412)
Any possibly-related TEAE	165 (41.1)	204 (49.5)
Dizziness	29 (7.2)	28 (6.8)
Headache	26 (6.5)	23 (5.6)
Somnolence	21 (5.2)	29 (7.0)
Fatigue	19 (4.7)	18 (4.4)
Nausea	18 (4.5)	28 (6.8)
Gamma-glutamyltransferase increased	11 (2.7)	51 (12.4)
Hyponatraemia	10 (2.5)	4 (1.0)
Vertigo	8 (2.0)	12 (2.9)
Vomiting	8 (2.0)	11 (2.7)
Weight increased	8 (2.0)	14 (3.4)
Alanine aminotransferase increased	2 (0.5)	9 (2.2)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; IMP = investigational medicinal product; N = number of subjects in the analysis set; TEAE = treatment-emergent adverse event.

Incidences of nausea and increased GGT were notably lower in the ESL group (>2% difference between groups), whereas hyponatraemia occurred more often in the ESL group compared to CBZ-CR (2.5% vs. 1%).

TEAEs by intensity

The majority of subjects reported TEAEs that were mild in both treatment groups (69.6% and 71.4% of ESL and CBZ-CR subjects, respectively). The rates of moderate and severe events were similar for both groups.

- *Supportive study pool (conversion-to-monotherapy studies 045 and 046)*

Overview of TEAEs

A total of 287 of the 365 subjects (78.6%) in the conversion-to-monotherapy trials reported TEAEs. TEAEs were reported at a higher incidence in the 1600 mg dose group compared to the 1200 mg dose group (81.4% [197/242] and 73.2% [90/123], respectively). Severe and serious TEAEs revealed a similar pattern (6.6% [16/242] each in the 1600 mg dose group vs 4.1% [5/123] each in the 1200 mg dose group). Discontinuation due to TEAEs was almost twice as high in the 1600 mg dose group compared to the 1200 mg dose group (15.3% [37/242] vs. 8.1% [10/123]).

In study 045 more subjects on 1600 mg ESL had a TEAE leading to dose reduction compared to the 1200 mg dose group (9.4% vs. 4.6%). In study 046, more subjects on 1200 mg ESL had a TEAE leading to dose reduction compared to 1600 mg (5.2% vs. 3.5%).

TEAEs by SOC and PT

The most commonly reported TEAEs (≥10% of subjects in either treatment group) were in line with those

seen in study 311 for the following SOCs: nervous system disorders, gastrointestinal disorders, infections and infestations, general disorders and psychiatric disorders. They were headache, dizziness, fatigue, somnolence, nausea, and back pain.

Somnolence was reported in 6.7% of ESL treated subjects and in 8.3% of CBZ-CR treated subjects. The incidence was ≥5% higher in the 1600 mg dose group (13.6%) compared to the 1200 mg dose group (7.3%). A higher incidence in the 1600 mg dose group compared to the 1200 mg dose group was also found for the following TEAEs: *asthenia (2.9% vs. 0.8%), blood sodium decreased (2.5% vs. 0%), hypertension (3.3% vs. 0.8%).*

- *Long-term open label extension study 050*

In study 050, the overall incidence of TEAEs (82.8%) was similar to the overall incidence for the monotherapy historical controlled study pool. The most-commonly reported TEAEs were headache (25.9%), dizziness (18.2%), nasopharyngitis (11.7%), fatigue (9.9%), back pain (8.0%), depression (8.0%), and fall (8.0%). The type and frequency of common TEAEs and medically-significant events (< 1% of subjects) were generally similar to those observed for the monotherapy historical controlled study pool.

Use of higher doses was associated with a similar overall pattern of AEs compared with the lower dose groups (representing 800, 1200, and 1600 mg average doses). In the 3 highest dose groups, the rates for "any TEAE" were not dose-related: 91.2% (1000 to < 1400 mg), 78.1% (1400 to < 2000 mg), and 84.4% (≥ 2000 mg). Only headache (20.6%, 24.1%, and 27.8% of subjects, respectively) and blurred vision (2.9%, 4.4%, and 5.6% of subjects, respectively) showed a small dose response (i.e., an increase in incidence across increasing ESL modal daily dose categories).

Serious adverse event / deaths / other significant events

Deaths

Overall, 5 subjects died during the three Phase 3 studies. None of the deaths was considered related to ESL.

In study 311, 4 subjects (2 in the ESL group [0.5%] and 2 in the CBZ-CR group [0.5%]) died due to TEAEs:

- A 61 year old male on ESL 400 mg QD with glioblastoma multiforme, diagnosed 12 days after treatment initiation with ESL, discontinued ESL and died on Day 74. This condition may have been present as underlying disease triggering seizures.
- A 63 year old male on ESL 800 mg QD died due to cardiac arrest on Day 97. The subject was reported to have had multiple underlying cardiac risk factors. The event was considered unrelated to ESL.
- A 56 year old male on CBZ-CR 200 mg BID committed suicide on Day 35. No history of suicidal history. Hence, the event was considered possibly related to treatment (suicidal risk is a class effect of AEDs)
- A 71 year old male on CBZ-CR 200 mg BID was diagnosed with lung adenocarcinoma on Day 43 and died 2.5 years later. The event was considered unrelated to CBZ-CR and present as an underlying condition.

In the supportive studies 045 and 046, there was one death in the ESL 1200 mg dose group due to multiple injuries following a road traffic accident considered not related to treatment.

In study 050, there were two on-treatment deaths (metastatic non-small cell lung cancer with pneumonia, and sudden unexplained death in epilepsy [SUDEP]). In addition, there was 1 post-treatment SUDEP. The death cases were considered not related to study drug or treatment.

Serious Adverse Events (SAEs)

In the pivotal study 311, the incidence of serious TEAEs was similar in the ESL group (10.0%) and the CBZ-CR group (10.9%). Serious TEAEs reported by >1 subject in the ESL group were status epilepticus (0.7%), craniocerebral injury (0.5%) and epilepsy (0.5%). In the CBZ-CR group, syncope (1.0%), convulsion (0.7%), appendicitis (0.5%), atrial fibrillation (0.5%), head injury (0.5%), inguinal hernia (0.5%), partial seizures (0.5%) and pulmonary embolism (0. 5%) were reported by >1 subject.

In the supportive studies 045 and 046, the most commonly reported serious TEAE (≥1 subject in any treatment group) was hyponatraemia (1600 mg: 1.2%, 1200 mg: 0%). In the open-label extension study 050 the type of SAEs was generally similar, but as expected the frequency of SAEs was higher (16.8%) compared to the monotherapy historical controlled study pool (5.8%) due to the difference in duration of the studies.

TEAEs of special interest

TEAEs of special interest included events known to be particularly relevant to treatment with AEDs, and were defined as follows:

- Study 311: TEAEs of special interest were defined using the following standardised MedDRA queries (SMQs): behavioural/psychiatric events, central nervous system events, severe cutaneous adverse reactions, cerebrovascular disorders, agranulocytosis, dyslipidaemia, haemopoietic cytopenias, depression and suicide/self-injury, haemorrhages, cardiac arrhythmias, torsade de pointes/QT prolongation, neurological AEs, and hyponatraemia. In addition, hepatic disorder TEAEs (as defined by the SMQ “drug-related hepatic disorders”) were presented.
- Pooled studies 045 and 046: medically significant events included allergic reactions (including rash and hypersensitivity), suicide attempt, elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to 3 × upper limit of normal (ULN), hypothyroidism.

In study 311, frequencies for neurological adverse events, neurological disorders, behavioural/psychiatric events, depression and suicide/self-injury, mental impairment disorders, haematopoietic cytopenias, seizures, agranulocytosis, cerebrovascular disorders were similar for both treatment groups.

There was a higher incidence (≥2% more) in the ESL group compared to the CBZ-CR group for the SMQs headaches (ESL: 27.9%, CBZ-CR: 24.0%), haemorrhages (ESL: 9.0%, CBZ-CR: 7.0%), hyponatraemia (ESL: 4.5%, CBZ-CR: 1.5%) and movement disorders (ESL: 3.7%, CBZ-CR: 1.7%).

There was a higher incidence (≥2% more) in the CBZ-CR group compared to ESL for the SMQs behavioural/psychiatric events (ESL: 15.2%, CBZ-CR: 18.2%), cardiac arrhythmias (ESL: 6.7%, CBZ-CR: 10.2%), dyslipidaemia (ESL: 4.5%, CBZCR: 7.0%) and QT prolongation (ESL: 2.5%, CBZ-CR: 4.6%). Hepatic disorder TEAEs were analysed separately and found to have higher incidences in the CBZ-CR group compared to ESL (19.7% vs. 10.2%). The difference was most pronounced for GGT increased (CBZ-CR: 14.8% vs. ESL: 4%).

TEAEs in the SOC skin and subcutaneous tissue disorders were reported for 11.2% of ESL subjects and 15.0% of CBZ-CR subjects including rash (3.2% of ESL subjects and 2.9% CBZ-CR subjects) and allergic dermatitis (0.5% of ESL subjects and 2.4% of CBZ-CR subjects). Severe cutaneous adverse reactions were observed in 4 (1.0%) and 8 (1.9%) patients in the ESL and CBZ-CR group, respectively. Cutaneous TEAEs (including all PTs of the SOC “skin and subcutaneous tissue disorders”, and the PTs “drug hypersensitivity” and “hypersensitivity” from the SOC “immune system disorders”) assessed as at least possibly related by the investigator occurred in 6.2% and 8.7% of the ESL and CBZ-CR patients, respectively.

In studies 045 and 046, the incidence of allergic reactions, including rash and hypersensitivity (overall 5.8%) was comparable between dose groups. In study 046, 7 subjects have been reported with at least one

rash-related TEAE with a majority (all but one) of subjects receiving 1600 mg ESL. There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. There was 1 case with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) identified by the investigator. Two serious TEAEs resulted in discontinuation (rash pruritic and DRESS). One subject in the 1200 mg dose group reported a TEAE of suicidal ideation.

Based on the C-SSRS, 1 subject (also in the 1200 mg dose group,) had an aborted suicide attempt; no suicide-related TEAE was reported for this subject.

Two subjects (0.8%) reported elevations of AST and/or ALT to >3 × ULN. Both subjects received ESL doses of 1600 mg (rated as clinically significant in one of these subjects).

Hypothyroidism was reported in 3 ESL-treated subjects (0.8%) in the 1600 mg group. Subjects had a medical history of thyroid disease or baseline abnormalities.

Laboratory findings

Clinical laboratory evaluations included measurement of biochemistry, haematology, coagulation, thyroid function, bone turnover markers and urinalysis parameters. Parameters were classified as normal or abnormal according to the laboratories normal ranges and as clinically significant according to pre-specified significance criteria.

In study 311, main changes and differences between treatment groups in biochemistry parameters have been reported for GGT and bilirubin. Individual clinically significant abnormalities (as defined by the investigator) were generally low and comparable between treatment groups.

Total bilirubin decreased over time with larger mean decreases in the CBZ-CR group compared to the ESL group at most post-baseline visits. However, values were still within the normal range at all visits for the majority of subjects in both treatment groups (>94%). Differences in total bilirubin >ULN [Grade 1] were reported for 4.3% of subjects in the ESL group compared to 1.7% of subjects in the CBZ-CR group. Values >1.5x ULN (Grade 2) were also found more frequently in subjects on ESL compared to CBZ-CR (1.3% vs. 0.2%). Clinically significant total bilirubin values (as defined by the investigator) at any post-baseline visit were reported for 1.0% of ESL treated subjects compared to none in the CBZ-CR group. This finding somewhat contradicts reports of values over time indicative of a decrease in total bilirubin, which was more pronounced in the CBZ-CR group.

Regarding hepatic dysfunction, there was no additional concern related to transaminases increases of ALT, AST or alkaline phosphatase with frequency of significant values similar in ESL and CBZ-CR groups (≤3% in either group). Combined elevations of hepatic parameters were low without relevant differences. There were also no relevant differences between treatment groups for ALT or AST >3 × ULN together with TEAE data.

GGT was within the normal range for 86.8% of ESL subjects and 85.2% CBZ-CR subjects at baseline and above the normal range for 13.4% of ESL subjects and 14.2% of CBZ-CR subjects. At the final evaluation/early discontinuation visit, 21% of ESL subjects had a value above the normal range whereas 50% of CBZ-CR subjects had a value above the normal range. A total of 40 subjects (10.0%) in the ESL group compared to 116 (28.2%) in the CBZ-CR group had a change to an abnormally high value for GGT at endpoint. Individual clinically significant changes (as defined by the investigator) were reported for 7.1% of subjects from the ESL group and 18.2% of subjects in the CBZ-CR group).

Mean sodium levels were within the normal range. However, changes from baseline to lower values were more pronounced in patients receiving ESL compared to CBZ-CR. At final evaluation/early discontinuation visit, 8.2% of ESL subjects had a value below the normal range whereas only 2% of CBZ-CR subjects had a value below the normal range. The majority of subjects in both the ESL group (91.9%) and the CBZ-CR group (97.7%) had sodium values >130 mEq/L. Sodium decrease from baseline of >10 mEq/L was seen in

11.1% of ESL-treated subjects compared to 3.4% of CBZ-CR-treated subjects. Sodium levels ≤125 mEq/L were found in 1.5% of subjects in the ESL group and 0.2% in the CBZ-CR group. A shift in sodium levels from normal at baseline to low at endpoint was reported for 12 (3%) subjects on ESL and 5 (1.2%) of subjects on CBZ-CR. Clinically significant values for sodium at any post baseline evaluation were found for 4.3% of subjects on ESL and 1.5% of subjects on CBZ-CR. An overview of different sodium levels by dose groups is provided in Table 14.

Table 15 – Hyponatremia/Sodium Levels by Treatment Group and Individual Dose – Study 311 (Safety Set)

Sodium level	Statistic	ESL-Rand			CBZ-CR-Rand		
		800 mg QD (N=387)	1200 mg QD (N=130)	1600 mg QD (N=60)	200 mg BID (N=392)	400 mg BID (N=95)	600 mg BID (N=34)
>135 mEq/L	n (%)	323 (83.5)	100 (76.9)	42 (70.0)	362 (92.3)	80 (84.2)	27 (79.4)
130 - ≤135 mEq/L	n (%)	48 (12.4)	19 (14.6)	9 (15.0)	26 (6.6)	14 (14.7)	3 (8.8)
125 - ≤130 mEq/L	n (%)	13 (3.4)	9 (6.9)	7 (11.7)	4 (1.0)	0 (0.0)	4 (11.8)
≤125 mEq/L	n (%)	3 (0.8)	2 (1.5)	2 (3.3)	0 (0.0)	1 (1.1)	0 (0.0)
Any decrease from Baseline >10 mEq/L	n (%)	21 (5.4)	14 (10.8)	10 (16.7)	7 (1.8)	3 (3.2)	4 (11.8)

CBZ-CR = carbamazepine controlled-release; ESL = eslicarbazepine acetate; N = number of subjects with any post-baseline sodium assessment; n = number of subjects with minimum post-baseline value within the category; Rand = Randomised Treatment Group.

No clinically relevant changes over time or differences between the treatment groups were observed for the parameters of haematology, coagulation, thyroid function, urinalysis or bone turnover markers.

As for changes at an individual level, any change from a normal laboratory value at baseline to an abnormally low or high value post-baseline was found with similar frequency between treatment groups. Abnormalities (difference of ≥5% between treatment groups) have been reported for GGT (see above) as well as for chloride, whereby 75 subjects (18.7%) in the ESL group compared to 45 (10.9%) in the CBZ-CR group had a change to an abnormally low value for chloride at endpoint.

Furthermore, statistically significant differences between treatment groups when considering any post-baseline visit under the last evaluated dose were observed for chloride (2.0% of ESL subjects versus 0% of CBZ-CR subjects), HDL-cholesterol (0.5% of ESL subjects versus 2.7% of CBZ-CR subjects), sodium (4.3% of ESL subjects versus 1.5% of CBZ-CR subjects) and platelets (0.3% of ESL subjects versus 2.0% of CBZ-CR subjects).

In studies 045 and 046, there were no apparent changes of clinical significance from baseline to the lowest or highest on-treatment values for the haematology, serum chemistry (including lipid parameters or bone-turnover markers), urinalysis or coagulation parameters for either ESL dose group. This is also valid for sodium.

Since no comparator was included in these studies, results were most of all valuable for judging the frequency of abnormalities at the different doses. Abnormally low sodium levels of clinical significance post-baseline have been found in 4.1% of subjects on 1200 mg ESL and in 7% of subjects on 1600 mg ESL. Overall, the incidences were low for the minimum post-baseline sodium level categories of ≤125 mEq/L (3.3%), >125 to ≤130 mEq/L (7.0%) and for decreases from baseline >10 mEq/L (7.8%). Incidences were similar across both ESL dose groups for each minimum sodium category.

Vital signs and physical findings

In study 311, no clinically relevant vital signs changes over time or differences between treatment groups in

terms of systolic and diastolic blood pressure, pulse rate, body weight or BMI have been reported. The incidence of clinically relevant vital sign findings at post-baseline visits was similar to the baseline incidence in each treatment group and no differences were found between treatment groups (ESL: 7.8%, CBZ-CR: 10.6%). Results were similar when considering clinically relevant findings at any dose given during the study. The assessment of physical examination findings revealed fewer subjects on ESL compared to CBZ-CR with worsening from baseline to post-baseline mainly due to assessment of skin (3.6% vs. 7.5%).

The supportive study pool (studies 045 and 046) did not reveal additional issues. The only potentially clinically significant values, which have been noted, were high weight with a change from baseline ≥7% (1600 mg: 9.2%, 1200 mg: 2.5%) and low weight with a change from baseline ≤-7% (1600 mg: 2.9%, 1200 mg: 4.9%).

ECGs showed similar incidences of clinically relevant abnormalities for both treatment groups in study 311 (ESL: 3.0%, CBZ-CR: 3.2%). First degree atrioventricular block developed post-baseline in 2 subjects in the ESL group and 3 subjects in the CBZ-CR group. No additional concern derived from the supportive studies. Changes in parameters were similar for both dosing groups.

The incidence of worsening of neurological examinations findings post baseline was low with no relevant differences between treatment groups in either the pivotal study 311 or the supportive study pool.

Other observations related to safety

Suicidality was assessed as per C-SSRS and found to be low in terms of ideation and behaviour in both treatment groups in study 311. The incidences of suicide-related events were also low and similar between treatment groups. A total of 3.5% of ESL subjects and 3.4% of CBZ-CR subjects reported improvement in suicidal ideation at the end of the study. One subject committed suicide in study 311 while receiving CBZ-CR (considered possibly related to treatment).

In the supportive study pool, there were no completed suicides. The overall incidence of any suicidality (i.e. at least 1 occurrence of suicidal behaviour or ideation) was 3.6%; incidence of baseline suicidality was 1.6%.

Safety in special populations

Extrinsic or intrinsic factors have not been formally evaluated in study 311 but have been analysed in the supportive conversion-to-monotherapy study pool:

Intrinsic factors comprised age, gender, race, ethnicity, and weight. Most subjects were in the age group 18 to 65 years, and hence, no comparison between different age groups was conducted. In regard to gender (balanced), more TEAEs have been reported for females than for males (83.7% vs. 73.1%). None of the common TEAEs/laboratory parameters/vital signs/ ECG parameters differed by more than 10% across gender categories.

Race was predominantly Caucasians. Blacks and other race groups had similar overall frequencies of TEAEs and only few TEAEs differed in frequency by more than 10% across races (dizziness, fatigue).

There was no indication for a particular safety risk associated with ESL treatment in different weight categories.

Extrinsic factors comprised effect of the number of baseline AEDs and of the use of baseline AEDs on the safety profile of ESL. Differences in the incidences of overall and common TEAEs across a number of baseline AEDs and baseline AED use/non-use (except oxcarbazepine) were generally small, exhibited no meaningful patterns and were not considered clinically meaningful. Co-administration of ESL and oxcarbazepine was associated with a greater incidence of individual TEAEs than ESL alone and the difference was more than 10% for dizziness (50.0% vs. 19.8% for oxcarbazepine users/non-users) and vomiting (22.7% versus 5.2% for oxcarbazepine users/non-users).

No new information derived for use of ESL in pregnancy and lactation. Overdose (accidental) was reported in the US study pool (n=2 subjects) and confirmed available data on ESL overdose in subjects with adjunctive ESL treatment.

Discontinuation due to adverse events

In study 311, overall, fewer subjects discontinued ESL treatment (13.5%) compared to CBZ-CR (18.0%). TEAEs leading to discontinuation of study drug were reported for 11.8%, 24.3%, and 8.3% of subjects treated with 800 mg, 1200 mg, and 1600 mg ESL. In contrast, 18%, 19.7%, and 14.7% of subjects treated with 200 mg BID, 400 mg BID, and 600 mg BID CBZ-CR were reported to have discontinued study. Adverse events leading to discontinuation in more than 2 subjects in either treatment group were fatigue (7 and 3 patients on ESL and CBZ-CR, respectively), nausea (5 and 5 patients on ESL and CBZ-CR, respectively), dizziness and rash (each 4 and 4 patients on ESL and CBZ-CR, respectively), disturbances in attention (3 patients on ESL), somnolence (3 and 3 patients on ESL and CBZ-CR, respectively), dermatitis allergic (2 and 7 patients on ESL and CBZ-CR, respectively), headache (2 and 6 patients on ESL and CBZ-CR, respectively), convulsion (1 and 4 patients on ESL and CBZ-CR, respectively), GGT increased (1 and 3 patients on ESL and CBZ-CR, respectively), and hypersensitivity (4 patients on CBZ-CR). No subjects in the ESL group discontinued due to hyponatraemia.

In studies 045 and 046, the overall incidence of TEAEs resulting in discontinuation was higher in the 1600 mg ESL group than the 1200 mg group (1600 mg: 15.3%, 1200 mg: 8.1%). The most commonly reported TEAEs resulting in discontinuation (>2 subjects overall) were complex partial seizures (1600 mg: 2.1%, 1200 mg: 0.8%), hyponatraemia (1600 mg: 1.2%, 1200 mg: 1.6%), depression (1600 mg: 1.2%, 1200 mg: 0%) and nausea (1600 mg: 0.8%, 1200 mg: 0.8%).

In study 050, the type of TEAEs resulting in discontinuation was similar compared to the monotherapy historical controlled study pool, but frequencies were lower for the extension study (8.0%) than for the monotherapy historical controlled study pool (12.9%). The only TEAEs resulting in discontinuation reported by more than 1 subject were partial seizures with secondary generalization (2 [0.7%] subjects) and depression (2 [0.7%] subjects).

Post marketing experience

Patient exposure to marketed Zebinix, Exalief and Aptiom was estimated on the basis of worldwide ex-factory sales for the period from the time of marketing authorisation until 31-Aug-2015. During this period, ex-factory cumulative amounts reached a total of 33,289,762 units (1 unit = 1 tablet) sold and delivered in 22 countries. As of 21-Oct-2015, the estimated patient exposure was 1,109,658 patient-months.

ESL safety data from post-marketing sources (including 9 periodic safety update reports [PSURs] since first approval of ESL) remains in accordance with cumulative experience during clinical development. Cumulatively, 702 serious and 1273 non-serious adverse drug reactions (implied causality) from health authorities, literature and spontaneous reports and 47 serious adverse reactions from post-marketing non-interventional studies were received. The most common adverse drug reactions were reported in the SOCs nervous system disorders (22.3%), general disorders and administration site conditions (13.5%), injury, poisoning and procedural complications (11.5%), metabolism and nutrition disorders (10.6%), skin and subcutaneous tissue disorders (8.5%), psychiatric disorders (7.4%), and gastrointestinal disorders (6.5%). The most commonly reported adverse reaction terms were hyponatraemia (9.5%), seizure (5.3%), dizziness (4.1%), rash (2.6%), fatigue (2.1%), and nausea (1.8%).

2.5.1. Discussion on clinical safety

ESL is already indicated as adjunctive therapy for the treatment of POS in adult epilepsy patients at doses of up to 1200 mg/day for which safety has been previously evaluated. The safety profile of ESL as POS monotherapy was largely derived from the results of the pivotal trial 311 supporting the present application. Patients had completed a 1-week titration period and a 26-week evaluation period. An additional 26-week maintenance period was still ongoing, and was completed by 59.9% of ESL subjects and 64.1% of CBZ-CR subjects. In addition, supportive data from two pooled conversion-to-monotherapy studies (045 and 046) were provided. In all three studies, patients could receive ESL up to a maximum daily dose of 1600 mg. However, no integrated analysis of the safety data was performed due to differences in study design of the pivotal and the supportive studies as well as differences in the indication. Finally, during the course of this procedure, the MAH provided additional data from a long term open label extension study (study 093 050), which enrolled subjects from studies 045 or 046, to further support the (long-term) safety of the new proposed maximum dose of ESL 1600 mg/day.

In the pivotal study 311, the overall incidence of TEAEs was similar in both treatment groups (75.3% vs 77.7% in the ESL and CBZ-CR group, respectively). ESL was found slightly favourable over CBZ-CR for at least possibly related TEAEs and TEAEs leading to discontinuation (41.1% vs. 49.5% and 13.5% vs. 18%). The frequency of SAEs was similar in both groups (10% for ESL vs 10.9% for CBZ-CR). Two deaths occurred in each treatment group.

Under certain circumstances, concomitant AED treatment was allowed in study 311 (during down-titration after discontinuation; benzodiazepines ≤ twice a week). More subjects on higher ESL dose levels (B and C) in study 311 used concomitant AEDs compared to those on CBZ-CR. The MAH clarified that the overall incidence in TEAEs did not significantly change when TEAEs that occurred during the intake of any new AED were excluded (other than an expected slight decrease).

The data from study 311 (laboratory analyses including values over time, shift analyses, clinically significant laboratory values) point towards a more pronounced decrease in sodium with ESL compared to CBZ-CR albeit most of the subjects presented with sodium levels >130 mEq/L (>90%). The same trend was observed for cases of hyponatraemia albeit the total number of TEAEs was low (ESL: 3% vs. CBZ-CR: 1%) and comparable with the incidences seen in the adjunctive treatment program of ESL. The combined incidence of ADRs (TEAEs assessed as at least possibly related by the investigator) of hyponatraemia and blood sodium increased amounted to 3.7% (ESL) and 1.5% (CBZ-CR). A clear ESL dose relationship was seen for cases of hyponatraemia. A similar observation as made in the supportive conversion-to-monotherapy study pool.

At the same time, ESL appears more favourable than CBZ-CR regarding liver enzyme increases, most of all depicted as '*GGT increased'*. The incidence of increases of GGT was more than 10 times higher with CBZ-CR than with ESL (14.6% versus 4%). At the same time, there was a slightly higher number of subjects with clinically significant abnormally total bilirubin values in the ESL group compared to CBZ-CR (1% versus 0%), although overall, a decrease in total bilirubin was observed in both groups over time. Generally, mean laboratory values over time did not raise any new concerns with ESL but supported TEAEs reported in the monotherapy study program. Likewise, findings for vital signs and from physical examinations remained unremarkable. Intrinsic and extrinsic factors have not been evaluated for the pivotal study 311 and hence it is not known if for example higher age relates to a higher incidence of certain types of TEAEs.

An analysis of adverse events of special interest for ESL and antiepileptic drugs in general yielded results in accordance with the overall picture of TEAEs i.e. an advantage of ESL over CBZ-CR in hepatic disorder TEAEs (as per SMQ) and a slight disadvantage of ESL over CBZ-CR in hyponatraemia (as per SMQ). In the supportive conversion-to-monotherapy study pool, analyses of TEAEs of special interest revealed ESL to be favourable over CBZ-CR for psychiatric events, cardiac-related events and dyslipidaemia, whereas

headache, haemorrhages, hyponatraemia, and movement disorders were slightly more pronounced with ESL compared to CBZ-CR. Furthermore, while the incidence of allergic reactions seemed to be balanced between ESL dose groups, in study 046, 7 subjects experienced at least one rash-related TEAE with a majority (all but one) in subjects receiving 1600 mg ESL. Two of these events were serious in nature (including one event of DRESS) and considered probably related to ESL.

Based on the review of the monotherapy study data, the safety of ESL was largely consistent with the known safety profile in the adjuvant treatment setting. The most common adverse reactions with ESL as add-on treatment for POS are dose-related and belong to the SOCs nervous system disorders and gastrointestinal disorders including dizziness, somnolence, headache and nausea. The most common TEAEs reported for ESL in POS monotherapy were in line with those already identified for the adjunctive setting.

As data from the double-blind part of study 311 could not be fully integrated with the data from the add-on epilepsy studies given that the comparator was not placebo, but active substance, the MAH performed a direct comparison of both safety data sets. For the purpose of providing up-to-date information in section 4.8 of the SmPC, ADRs that occurred at a similar incidence in monotherapy and adjunctive treatment studies (vision blurred, hypotension, diarrhoea, dyspepsia, skin disorder, fatigue, asthenia and blood chloride decreased) were kept unchanged. In addition, the MAH proposed to keep frequency categories as already delineated based on adjunctive treatment for ADRs, which occurred with lower frequency in the monotherapy studies (including dizziness, decreased appetite, gait disturbance). No ADRs from the SOCs immune system disorder, cardiac disorders, respiratory, thoracic and mediastinal disorders, hepatobiliary disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders had been reported more than once in monotherapy studies and hence, ADRs listed in these categories remained unchanged based on adjunctive treatment experience. For the ADRs anaemia, hypothyroidism, memory impairment, and blood sodium decreased, which occurred at a higher incidence in the monotherapy studies compared to adjunctive treatment studies, the frequency category remained the same (‘uncommon’) when being calculated in the overall safety database.

Unexpected adverse events in the monotherapy study program included 2 cases of overweight in subjects on ESL compared to no subject on CBZ-CR. Both cases were non-serious and mild and causality was considered either unlikely or possibly related. In both subjects the event first started after at least 6 months of continuous treatment with ESL and the event resolved or did not worsen even with continuation of ESL treatment. Similarly, contusion was found to occur in 2 ESL treated subjects in monotherapy studies and in no subject on CBZ-CR. Both events resolved without dose adjustment and were non-serious. Furthermore, there were 2 reports of suicidal ideation in patients receiving ESL and 1 report in a patient on CBZ-CR. The subjects on ESL experienced the event in the context of depression or depressive episodes. No further event has been reported in the integrated safety database that comprise all completed clinical trials in epilepsy (adjunctive therapy and monotherapy ESL clinical trials), in a total 2434 exposed patients. In addition, the MAH provided a C-SSRS assessment showing that the incidences of suicide-related events were low and similar between treatment groups. Overall, the CHMP considered that the safety information in the SmPC including a warning in section 4.4 in relation to suicidality were still adequate and no update was needed in relation to the aforementioned adverse events.

The CHMP furthermore noted 3 cases of anxiety reported with ESL in study 311 (0.7%) with a total of 10 cases in the overall safety database of ESL. Although the 3 new cases were non-serious and self-limited, given that ESL is known to cause adverse reaction within the SOC Psychiatric disorders that refer to the MedDRA high level term anxiety disorders, such as nervousness and agitation, which are already captured in the ESL SmPC, the CHMP was of the view that anxiety should be added to SmPC section 4.8 as uncommon adverse reaction.

During the safety assessment, emphasis was placed on the new proposed maximum daily dose of 1600 mg ESL. The MAH’s rationale for evaluating 1600 mg ESL QD in the monotherapy setting was mainly based on

safety results of this ESL dose in other indications and assumptions that tolerability of ESL may be better when given as monotherapy compared to adjunctive treatment.

Notably, since the study design of the pivotal study 311 allowed up-titration according to seizure severity, subjects were not evenly distributed between dose groups. Only 15% of subjects (60 out of 401 patients in the ESL group) received 1600 mg/day in dose group C, whereas all other subjects only received ESL doses up to 1200 mg/day (dose group A or B), for which safety had already been established in the add-on setting. Overall, 25 of 60 subjects (41.7%) have been treated with ESL 1600 mg/day for 6 months and 16 of 60 subjects (26.7%) received ESL for at least 12 months. This low number of patients hampers the safety assessment of the new proposed maximum dose and of a possible dose relationship of TEAEs. In addition, treatment duration in the higher dose groups B and C was shorter for ESL compared to CBZ-CR, mainly due to a higher rate of discontinuations due to lack of efficacy and withdrawal of consent.

When comparing TEAEs reported for the different dose groups A, B, and C in study 311, there was a trend towards dose-related increases in the incidences of some of the AEs including abdominal pain, abdominal pain upper, asthenia, fatigue, malaise, fall, aspartate aminotransferase increased, blood creatine phosphokinase increased, memory impairment, tremor, depressed mood, and mood altered. Differences between treatment groups at dose level C were also observed with regards to serious TEAEs which have been reported in 15% of subjects from the 1600 mg ESL dose and for 2.9% of subjects on the equivalent CBZ-CR dose level. However, the MAH explained that only 2 of the serious TEAEs were considered to be possibly related to study drug. These two events were both observed in a single subject and clearly correlated with ESL. Amongst the remaining 7 SAEs, 3 could probably have been related to ESL, i.e. SAE of Adams-strokes syndrome and additionally SAE Atrioventricular block complete in a single subject, and a suicide attempt in another subject. Taken together, there was insufficient evidence from these cases to support a different safety profile for the highest dose group.

Interestingly, a discrepancy in terms of dose-relationship was found in study 311 whereby TEAEs leading to discontinuation were lowest in the highest dose group C for both treatments, which is surprising especially against the background of a dose-related increase in discontinuations previously observed for Zebinix as adjunctive treatment. This finding could not be explained and it could not be excluded that it was a chance finding given the low number of patients in the highest dose groups

TEAEs in the supportive conversion-to-monotherapy study pool were reported with a higher incidence in the 1600 mg dose group compared to the 1200 mg dose group (81.4% vs. 73.2%). Furthermore, discontinuation due to TEAEs was almost twice as high in the 1600 mg dose group compared to the 1200 mg dose group (15.3% vs. 8.1%) and hyponatraemia was reported to be serious in 1.2% of subjects on 1600 mg in the supportive conversion-to-monotherapy study pool compared to no such event in the 1200 mg dose group. However, both studies were considered supportive only due to the open-label design while lacking an active comparator or placebo. Furthermore, due to the short study duration (18 week treatment period) data from the supportive conversion-to-monotherapy study pool did not contribute to the long-term experience with ESL 1600 mg/day. Data from the long-term open label extension of studies 045 and 046 (study 050) were thus provided by the MAH to address the concerns of the CHMP. In this extension, patients received ESL doses up to 2400 mg/day. The flexible dosing in this study allowed for stating modal daily doses only. The most common modal daily dose including the 1600 mg dose was administered for more than one year in 190 subjects and for more than 2 years in 113 subjects. No consistent increase was observed in the overall incidence of TEAEs across modal daily dose groups (91.2%, 78.1%, and 84.4% of the 1000 to < 1400 mg, 1400 to < 2000 mg, and ≥ 2000 mg dose categories, respectively). Furthermore, comparison of the highest modal daily dose groups 1400 mg to <2000 mg and ≥2000 mg ESL showed that few TEAEs increased across these two doses (e.g. vomiting, upper respiratory tract infection, fall, contusion, hyponatraemia), whereas no or an inverse relationship with dose was seen for other events. Overall, the CHMP was of the view that no firm conclusion could be drawn from these data.

Taken together, the available data point towards a safety profile of ESL 1600 mg/day, which is not significantly worse than the one of lower daily doses. From a safety point of view, there was hence no objection against the 1600 mg/day ESL dose to be administered in monotherapy of POS. However, the monotherapy study program encompassed only a limited number of elderly patients (aged ≥65 years). A total of 26 (6.5%) elderly patients have been exposed to ESL and 35 (8.5%) received CBZ-CR in study 311. A single subject was treated with the highest ESL dose of 1600 mg. Four additional subjects have been included in supportive study 045 to receive ESL 1600 mg/day. These limited data were considered by the CHMP to be insufficient in order to characterise the safety of ESL in the elderly population, and given that older patient may be more susceptible to AED induced (CNS) side effects, the CHMP was of the view that the 1600 mg dose could not be recommended for this population.

2.5.2. Conclusions on clinical safety

Overall, the available data indicate a similar safety profile of ESL in POS monotherapy compared to the already approved add-on indication in adult epilepsy patients with POS. Some uncertainties remained with regards to the new proposed maximum daily dose of 1600 mg ESL. The number of patients exposed to ESL doses of 1600 mg/day in the pivotal trial was limited which hampered the assessment of possible dose-related effects. However, taking into account the totality of the available data, there was no clear evidence of a worse safety profile of this dose compared to lower ESL doses (800 and 1200 mg). Therefore, the CHMP concluded that use of ESL doses up to 1600 mg per day in POS monotherapy was acceptable, except for elderly patients due to lack of experience in this patient group. When comparing ESL to CBZ-CR, a favourable profile was observed for ESL with regards to TEAEs possibly related to study medication, TEAEs leading to study discontinuation and liver enzyme (GGT) increases, whereas the risk of hyponatraemia was more pronounced with ESL than with CBZ-CR.

In conclusion, the CHMP was of the view that the available data were suitable to support the extension of indication of Zebinix to monotherapy of adult epilepsy patients with POS with or without secondary generalisation at ESL doses up to 1600 mg/day.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 22.0 (dated 02 March 2017) is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur updated assessment report is attached.

The CHMP endorsed the RMP version 22.0 (dated 02 March 2017) with the following content:

Safety concerns

Table 16 - Summary of the safety concerns

Important identified risks	• Hyponatremia • Cutaneous adverse reactions
Important potential risks	• Thyroid function changes • International Normalised Ratio (INR) and activated Partial Thromboplastin Time (aPTT) increase

	• Cardiovascular/cerebrovascular ischemia • Potential for suicidality as anti-epileptic drug • Bone disorders
Missing information	• Exposure during pregnancy • Pediatric population (< 2 years of age) • Elderly population • Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

Pharmacovigilance (PV) Plan

Table 17 - Ongoing and planned additional PhV studies/activities in the PV Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
BIA-2093-402 Pregnancy Exposure Registry (EURAP Registry) Category: 3	Observational Pregnancy Exposure Registry to detect any potential adverse fetal effects, including birth defects, in prospectively enrolled women exposed to ESL during pregnancy.	Exposure during pregnancy The study aims at investigating the potential harm to an unborn child if the mother uses Zebinix during pregnancy	Started.	Interim report expected by December 2017 Final report expected by December 2024

Risk Minimisation Measures (RMMs)

Table 18 - Summary of the RMMs

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks		
Hyponatremia	• Warning to monitor serum sodium levels before and during treatment with ESL; determine serum sodium levels if clinical signs of hyponatremia occur and during routine laboratory examination. If clinically relevant hyponatremia develops, ESL should be discontinued. • Listed as undesirable effect.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	• Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	
Cutaneous adverse reactions	• Warning to stop therapy in case of signs or symptoms of hypersensitivity; to screen and genetically test individuals of Han Chinese, Thai origin and other Asian populations at risk for HLA-B*1502 allele before starting treatment; to consider benefits of treatment for patients of European descent or Japanese origin, if they are known to be positive for HLA-A*3101. • Listed as undesirable effect. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic (including vasculitis, leukocytoclastic vasculitis and purpura). • Prescription only medicine.	None
Important potential risks		
Thyroid function changes	• Listed as undesirable effect. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None
International Normalised Ratio (INR) and activated Partial Thromboplastin Time (aPTT) increase	• Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None
Cardiovascular/cerebrovascular ischemia	• Included in safety monitoring in clinical studies. • Prescription only medicine. • Implemented as monitoring topic.	None
Potential for suicidality as anti-epileptic drug	• Warning to monitor patients for signs of suicidal ideation and behaviors and to consider appropriate treatment and/or to seek medical advice if signs of suicidal ideation or behavior emerge. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None
Bone disorders	• Implemented as monitoring topic (including osteocalcin increased, decreased bone mineral density, osteopenia, osteoporosis, and fracture). • Included in safety monitoring in clinical studies. • Prescription only medicine.	None
Missing information		

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Pregnancy	• Caution should be exercised when prescribing ESL to pregnant or lactating women. • Monotherapy should be preferred whenever possible as treatment to reduce risk of congenital malformation. • Specialist advice to be provided to women who are likely to become pregnant or who are of child-bearing potential. • No sudden treatment discontinuation should be undertaken as this may lead to breakthrough seizures. • Vitamin K1 should be administered in last few weeks of pregnancy and to newborn to avoid bleeding disorders in newborn. • Breastfeeding should be discontinued during treatment with ESL. • Alternative, effective and safe method of contraception in addition to oral contraception necessary; non-clinical studies have shown developmental effects in embryos. • Supplementation of folic acids before and during pregnancy to reduce possible contributory risk of fetal abnormality by anti-epileptic treatment. • Implemented as monitoring topic. • Included in a Pregnancy Registry (EURAP Registry).	None
Pediatric population (< 2 years of age)	• ESL is not recommended for use in children aged 6 years and below, as the safety and efficacy of ESL has not yet been established (in section 4.2 of the SmPC). • Studies BIA-2093-305 and BIA-2093-208 have been completed. • PIP (P/0197/2013; EMEA-000696-PIP02-M04) is ongoing. • Implemented as monitoring topic. • Prescription only medicine.	None
Elderly population	• Implemented as monitoring topic. • Prescription only medicine.	None
Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	• Ongoing monitoring of long term effects of ESL on brain development, learning, intelligence, growth, endocrine function, puberty and child bearing potential in children. • Implemented as monitoring topic. • Prescription only medicine.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes to SmPC sections 4.1 and 4.2 (additions are

shown in bold, deletions as strike-through) are summarised below:

SmPC section 4.1

Zebinix is indicated as:

- **monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;**
- adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

SmPC section 4.2

Posology

Adults

Zebinix may be taken as monotherapy or added to existing anticonvulsant therapy. The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1,200 mg once daily ~~(see section 5.1)~~. **Some patients on monotherapy regimen may benefit from a dose of 1,600 mg once daily (see section 5.1).**

Special populations

Elderly (over 65 years of age)

No dose adjustment is needed in the elderly population provided that the renal function is not disturbed. **Due to very limited data on the 1,600 mg monotherapy regimen in the elderly, this dose is not recommended for this population.**

Changes were also made to the product information to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as this variation did not lead to significant changes affecting the readability of the product information. Thus, the CHMP agreed that there was no need to perform a new readability test.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ESL has been authorised in the EU/EEA via the Centralised Procedure by Commission Decision in April 2009 for adjunctive therapy in adults with POS with or without secondary generalisation. In 2016, the indication was extended to children older than 6 years and a paediatric formulation (50mg/ml oral suspension) was introduced. With the present application, the MAH sought the extension of the indication to POS monotherapy in adult epilepsy patients.

Epileptic focal seizures/POS are characterised by abnormal, excessive or hypersynchronous neuronal activity originating in a discrete area of the cerebral cortex, which may later spread to involve both cerebral hemispheres causing secondary generalisation. First line treatment of patients with newly diagnosed POS consists of monotherapy with an AED and approximately 60% of epilepsy patients manage to attain long-term seizure freedom on a single AED (Stephen, 2012), which is the ultimate treatment objective. The remaining patients require adjunctive therapy with 2 or more AEDs, which is usually applied after two failed monotherapies.

3.1.2. Available therapies and unmet medical need

Several AED treatment options exist for POS monotherapy: CBZ, oxcarbazepine, lamotrigine, zonisamide, phenytoin, levetiracetam, topiramate, valproate, gabapentin and lacosamide. Monotherapy of epilepsy has certain advantages for patients when compared with adjunctive therapy including improved patient compliance as well as a decreased risk for drug interactions and better tolerability. Despite the availability of a number of treatment options for POS monotherapy, as some patients experience tolerability issues or insufficient efficacy on the first AED attempt, extending the range of treatment options would be valuable as it could help optimise individual therapy. Thus, there remains a therapeutic need for additional monotherapy options.

3.1.3. Main clinical studies

To support the present application, the MAH has conducted one pivotal efficacy and safety study 311. The study was a non-inferiority trial against the active comparator CBZ-CR in adult patients with newly diagnosed epilepsy experiencing POS, using stepwise fixed dose increments based on individual treatment response at 3 different dose levels, i.e. dose level A (ESL 800 mg QD, CBZ-CR 200 mg BID), level B (ESL 1200 mg QD or CBZ-CR 400 mg BID) and level C (ESL 1600 mg QD or CBZ-CR 600 mg BID). The primary efficacy variable was the proportion of subjects in the PP set who were classified as seizure free for the entire 26-week evaluation period at the last evaluated dose level. Subjects who dropped out during this 26-week period were considered as non-seizure-free in the primary analysis. The chosen design and endpoints of the pivotal trial were generally in line with the recommendations of the CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98Rev.2/Corr), and with CHMP scientific advice.

Supportive data were presented from two conversion-to-monotherapy studies (045 and 046) as well as their long-term open label extension (study 050).

3.2. Favourable Effects

The proportions of seizure free subjects at the last evaluated dose level during the 26 week evaluation period of study 311 were 71.1% (276/388) in the ESL and 75.6% (300/397) in the CBZ-CR group (PP set; ARD: -4.28, 95% CI: -10.3; 1.74). The lower limit of the 95% CI was greater than the pre-specified NI margin of -12%. Additional analyses of the primary efficacy variable with alternative assumptions on seizure risk in drop-outs suggest that the conclusion of NI would not critically depend on the seizure rate in the drop-outs.

Consistent results were shown after 1 year of treatment, with seizure free rates of 64.7% (251/388) in the ESL group and 70.3% (279/397) in CBZ-CR subjects (PP set; ARD: -5.46, 95% CI: -11.88; 0.97). An additional analysis of seizure-freedom during the maintenance period for subjects on a stable dose for at least 1 year in which subjects with insufficient treatment time were considered non-seizure free revealed a similar ARD of ESL compared to CBZ-CR of -5.09 with a lower limit of the 95% CI of -11.76.

Notably, throughout the efficacy analyses of seizure freedom, the lower bound of the 95% CI was consistently close to the -12% NI margin. The NI margin had been tightened following CHMP scientific advice and was set at -12% in line with ILAE guidance and assuming a 60% seizure freedom rate in the CBZ-CR arm as well as that a relative difference to CBZ-CR of 20% or less was acceptable (ILAE, 1998; Glauser et al., 2006; Glauser et al., 2013). In fact, as the actual seizure freedom rate in the CBZ-CR group was 75.6%, the -12% absolute difference for the NI margin corresponds to a relative difference of less than 20%.

The new proposed maximum dose of ESL 1600 mg QD exceeds the hitherto evaluated and approved maximum dose of ESL as adjunctive therapy. Unfortunately, the design of study 311 (up-titration to higher dose-levels depending on treatment response) did not allow conclusive assessment of dose response relationship and the fact that only 15% of ESL subjects were treated with 1600 mg ESL during study 311 made the interpretation of the data in this dose group difficult. However, the finding of a retention rate of 43.4% ESL subjects at the maximum dose level C (compared to 50% CBZ-subjects) during the evaluation period and 69.6% ESL patients (compared to 81.3% CBZ-subjects) when including the maintenance period, suggested that several of the subjects who were not seizure free at 1200 mg ESL per day did in fact profit from a further increase in ESL dose to 1600 mg/day.

3.3. Uncertainties and limitations about favourable effects

Whereas non-inferiority of ESL compared to CBZ-CR with the pre-specified margin of -12% has been robustly demonstrated in study 311, the efficacy analyses consistently showed a numerically smaller effect of ESL compared to CBZ. In the analysis of treatment failure (seizure risk) based on time to event analysis (Kaplan-Meier analysis and Cox regression), even statistically significant superiority of CBZ-CR versus ESL was observed (p=0.0002), with Kaplan-Meier estimates of seizure risk of 6% (CBZ) and 12% (ESL) at the end of the 6-month Evaluation Period and 11% (CBZ) and 19% (ESL) after 1 year. However, in the context of a population at risk of seizures (median baseline seizure frequency of 4 and 2 during 1 year and 3 months, respectively, before study enrolment), the resulting Kaplan Meier seizures freedom estimates of more than 80% during 1 year of treatment clearly indicate efficacy of ESL.

Seizures during the evaluation period tended to be more severe in the ESL compared to the CBZ-CR group: 32% (ESL) and 19 % (CBZ-CR) seizures were secondary generalised, 43% (ESL) and 26% (CBZ-CR) were complex partial and 23% (ESL) and 40% (CBZ-CR) were simple partial seizures. However, subgroup analyses by seizure type at baseline revealed similar rates of seizure-freedom in subjects with secondary generalised seizures as worst seizure type at baseline (ESL: 74.3% and CBZ-CR: 77%, respectively) as well as in subjects with secondary generalised seizures as most frequent seizure type at baseline (ESL: 75.5%; CBZ: 74.9%), which was reassuring.

In the subgroup of patients with > 4 seizures (during 3 months as well as 1 year) prior to enrolment a > 10% difference in seizure-free subjects was found in favour of CBZ-CR compared to ESL. Similarly, in the subgroup previously treated with an AED (for a maximum of 2 weeks), the difference in seizure-free subjects was >20% again favouring CBZ-CR. However, less than 30% study subjects had > 4 seizures within 3 months prior to enrolment only approximately 15% subjects had an AED prior to the study, the latter being considered only vaguely indicative of epilepsy severity. The respective results should thus be interpreted with caution and no clear indication of lower efficacy of ESL in subjects with more severe epilepsy could be concluded.

3.4. Unfavourable effects

Overall, the safety data from study 311 and the supportive conversion-to-monotherapy studies, including an interim analysis of extension study 050, indicate a safety profile of ESL in POS monotherapy consistent with the approved use as add-on therapy. Safety issues identified with ESL when used as adjunctive treatment of POS mainly comprises adverse reactions from the MedDRA SOCs nervous system disorders and

gastrointestinal disorders. The most common TEAEs are dizziness, somnolence, headache and nausea and a dose related increase in TEAEs has been observed. Important identified risks of ESL pertain to cutaneous adverse reactions and hyponatraemia.

In the pivotal monotherapy study 311, the most commonly reported TEAEs for ESL were headache (22.9%) and dizziness (13.7%). Somnolence occurred in 6.7% of ESL patients and with regards to gastrointestinal disorders, 7.7% of patients receiving ESL reported nausea. Cutaneous ADRs occurred in 6.2% of patients in the ESL group. Less TEAEs at least possibly related to study medication and TEAEs leading to discontinuation (41.1% versus 49.5% and 13.5% versus 18%) were reported for ESL compared to CBZ-CR. Furthermore, the incidence of liver enzyme increases, namely GGT increased, was more than 10 times higher with CBZ-CR than with ESL (14.6% versus 4%). At the same time, slightly more cases of hyponatraemia were observed with ESL compared to CBZ-CR (ADRs of hyponatraemia and blood sodium decreased were reported by 3.7% versus 1.5% of ESL and CBZ-CR patients).

While generally, the safety information in the SmPC was considered to be still adequate, anxiety was added as an uncommon adverse reaction to SmPC section 4.8 in light of 3 case reports with ESL in study 311 (0.7%), raising the total number of reported cases to 10 in the overall safety database of Zebinix. This finding was not unexpected given that ESL is known to cause adverse reaction within the SOC Psychiatric disorders that refer to the MedDRA high level term anxiety disorders, such as nervousness and agitation, which are already listed in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

In study 311, only 15% (60/401) of subjects in the ESL group reached the highest dose group C (1600 mg/day) proposed as the maximum dose for POS monotherapy treatment. The low number of exposed patients and the lack of a placebo comparator in regard to the highest dose group made it difficult to assess the safety at this dose level and in fact of any possible dose relationship of AEs. Treatment duration in dose groups B and C was found to be shorter for ESL compared to CBZ-CR patients due to a higher rate of discontinuations. Differences between treatment arms have been detected at dose level C for the reporting of serious TEAEs (15% of subjects on 1600 mg ESL dose and 2.9% of subjects on the equivalent CBZ-CR dose). The majority of these SAEs were however not considered related to ESL. Surprisingly, TEAEs leading to discontinuation were found to be lowest in the highest dose group C for both treatments, which was unexpected especially given that a dose-related increase in discontinuations has previously been observed in the clinical development program of Zebinix as adjunctive POS treatment. A chance finding could not be excluded.

Data from studies 045 and 046 were only considered supportive in light of the limitations inherent to the study design and short duration of treatment. The safety data were broadly in line with pivotal study 311. A discontinuation rate twice as high in the 1600 mg/day dose group compared to 1200 mg/day and slightly higher incidences of TEAEs at the highest dose were observed, but there was no clear dose relationship for most of the TEAEs. An interim analysis of the long-term open-label extension study 050 did not show a consistent increase in AEs across modal daily dose groups, either.

Overall, there was no clear indication that ESL daily doses of 1600 mg in POS monotherapy would be associated with a worse safety profile compared to lower doses.

Evaluation of intrinsic and extrinsic factors has not been conducted in study 311. For this reason, it was difficult to judge if age leads to a higher incidence of certain TEAEs. Only 6.5% patients on ESL and 8.5% on CBZ-CR were >65 years of age while being evaluated in study 311. Furthermore, only one single subject aged >65 years has been exposed to 1600 mg/day ESL in study 311 and 4 additional subjects received 1600 mg ESL in the supportive US studies. In light of this limited experience, use of ESL 1600 mg/day was not recommended in the elderly, which has been reflected in the SmPC.

3.6. Effects Table

Table 19 - Effects Table for Zebinix for to monotherapy of adult with POS with or without secondary generalisation

Effect	Short Description	Unit	ESL	CBZ-CR	Uncertainties / Strength of evidence	References
Favourable Effects						
Seizure freedom	Proportion of subjects who remained in the study(1) and were seizure free at the last evaluated dose - 24 weeks - 52 weeks(2)	%	 71.1 64.7	 75.6 70.3	The lower limit of the 95% CI was close to but always greater than the pre-specified absolute difference of -12% (24 weeks: -10.3; 1.74 and 52 weeks: -11.88; 0.97) Average risk difference: -4.28 Results on the FAS and sensitivity analyses were generally consistent with the primary analysis on the PP.	BIA-2093-311 CSR
Treatment failure	Kaplan Meier estimate for the rate of patients experiencing a seizure (time to 1st seizure) - 24 weeks - 52 weeks	%	 12 19	 6 11	Hazard ratio: 1.874, 95% CI: 1.348; 2.605 Log rank p-value for the global KM: 0.0002 Risk of seizure was twice as high for ESL compared to CBZ-CR.	
Treatment retention	Retention rate of seizure free subjects at the maximum dose level (ESL 1600 mg/day and CBZ-CR 1200 mg/day) - 24 weeks - 52 weeks	n/N (%)	 23/53 (43.4) 16/23 (69.6)	 16/32 (50.0) 13/16 (81.3)	Low number of patients requiring escalation to maximum dose level limits interpretability of the efficacy assessment.	
Unfavourable Effects						
Cutaneous adverse reactions	Incidence of ADRs(3)	%	6.2	8.7	Study 311 design and low exposure to the maximum dose hampered the safety assessment of ESL 1600mg/day.	BIA-2093-311 CSR
Hyponatraemia	Incidence of ADRs(4)	%	3.7	1.5		
Nervous system disorders	Incidence of TEAEs - headache - dizziness - somnolence	%	 22.9 13.7 6.7	 21.8 12.4 8.3		
GI	Incidence of	%	7.7	9.7		

Effect	Short Description	Unit	ESL	CBZ-CR	Uncertainties / Strength of evidence	References
disorders	TEAEs of nausea					
Liver disorders	Incidence of TEAEs of GGT increased	%	4.0	14.6		

ADR = Adverse Drug Reaction; CBZ-CR = Controlled-release carbamazepine; CI = Confidence Interval; CSR = Clinical Study Report; ESL = eslicarbazepine acetate; FAS = Full Analysis Set; GGT = Gamma-glutamyltransferase; GI = Gastrointestinal; PP = Per Protocol; PT = Preferred Term; SOC = System Organ Class; TEAE = Treatment-emergent adverse events.

ADRs were defined as TEAEs assessed as at least possibly related by the investigator.

(1) Subjects who dropped out during the analysis period were considered as non-seizure free.
(2) At data cut-off, the maintenance phase was completed by 59.9% ESL and 64.1% CBZ-CR subjects.
(3) Including all PTs in the SOC "skin and subcutaneous tissue disorders", the PTs "drug hypersensitivity" and "hypersensitivity" from the SOC "immune system disorders".
(4) Including PTs "blood sodium decreased" (SOC "investigations") and "hyponatraemia" (SOC "metabolism and nutrition disorders").

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy and safety of ESL has previously been demonstrated for treatment of adults with refractory POS as adjunctive treatment in 4 pivotal, placebo controlled studies at doses of 800 mg and 1200 mg, the respective add-on indication is approved since 2009 in the EU. In the pivotal trial supporting the extension of indication to POS monotherapy, 71.1% of the adult patients receiving ESL and 75.6% of the patients taking CBZ-CR completed the 6-months evaluation period and were seizure free for the entire time (PP set). The lower limit of the 95% CI (-10.3) was greater than the pre-specified absolute non-inferiority margin of -12%. Largely consistent results were shown in the sensitivity analyses, the relative risk difference as well as the analyses of seizure-free subjects after 1 year of treatment indicating maintenance of the effect. The proportions of seizure free subjects reported in study 311 were high, amounting to 88% in ESL and 94% in CBZ-CR subjects after 26 weeks of treatment and to 81% in ESL and 89% in CBZ-CR subjects after 1 year of treatment at stable dose in the Kaplan-Meier analyses. Given that this high rate of seizure freedom was achieved in a population at risk of recurrent seizures, whereby seizure freedom is the ultimate treatment goal, the results were considered clinically relevant and clearly indicative of a beneficial effect of ESL in POS monotherapy.

However, the vast majority of efficacy endpoints including risk of seizure at the last evaluated dose, completion rates as well as distribution of subjects across dose levels, indicate a consistent trend towards lower efficacy of ESL compared to CBZ-CR. In particular, the analysis of treatment failure (seizure risk) based on time to event analysis (Kaplan-Meier analysis and Cox regression) showed statistically significant superiority of CBZ-CR compared to ESL, whereby the risk of seizures was twice as high with ESL compared to CBZ-CR (12% versus 6%). This analysis was considered relevant by the CHMP as it is sensitive to show differences between treatments, and handling of missing values in this analysis was more appropriate than in the primary analysis. Thus, while non-inferiority at the pre-specified margin of -12% has been robustly demonstrated, the available evidence suggests slightly lower efficacy of ESL compared to CBZ-CR in the population studied.

Nevertheless, the CHMP acknowledged that ESL provides some advantages compared to CBZ-CR, including a more than 10% difference in AEs of GGT increase in direct comparison to CBZ-CR, suggesting a lower risk of liver disorders. Furthermore ESL has a low interaction potential and faster titration compared to most other AEDs is possible as well as once-daily administration.

Overall, the totality of clinical safety data of ESL in the studies evaluating its use as POS monotherapy supported a safety profile consistent with the profile established in the approved add-on setting. The most common adverse reactions remain nervous system disorders and gastrointestinal disorders including dizziness, somnolence, headache and nausea and the important identified risks of ESL are cutaneous adverse reactions and hyponatraemia. Uncertainties remained in the evaluation of safety of the new maximum dose for monotherapy, ESL 1600 mg/day, due to the limited exposure in the pivotal trial (only 15% of patients titrated to this dose and subjects on higher ESL doses had shorter treatment duration) and as the study designs of the monotherapy trials were not suitable to assess a possible dose-response relationship. However, the retention rates after 24 and 52 weeks in study 311 suggest that some patients gain additional benefit at this dose and tolerate it well.

3.7.2. Balance of benefits and risks

The available study data demonstrate a benefit of ESL as monotherapy for the treatment of POS in newly diagnosed epilepsy adult patients with more than 80% of patients achieving seizure freedom for a duration of 1 year. The benefits of ESL outweighed the risk of mainly nervous system disorders and gastrointestinal disorder. Therefore, the CHMP concluded that the benefit/risk balance of Zebinix as monotherapy in the treatment of POS, with or without secondary generalisation, in adults with newly diagnosed epilepsy was positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4. Recommendations

Outcome

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**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication for the tablet formulation to include the use of Zebinix as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy, in addition to the previously authorised indication as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet was updated in accordance. The MAH also took the opportunity to make editorial amendments throughout the product information.

Furthermore, the product information is being brought in line with the latest QRD template version.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

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 indication for the tablet formulation to include the use of Zebinix as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy, in addition to the previously authorised indication as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet was updated in accordance.

Furthermore, the product information is being brought in line with the latest QRD template version.

Summary

For further information, please refer to the scientific discussion Zebinix EMEA/H/C/000988/II/0053.