13 October 2016
EMA/728128/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zebinix

International non-proprietary name: eslicarbazepine acetate

Procedure No. EMEA/H/C/000988/X/0050/G

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
ANCOVA	analysis of covariance
API	Active Pharmaceutical Ingredient
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration-time curve
AV	atrioventricular
BMI	Body Mass Index
$c_{av,ss}$	Average plasma concentration at steady-state
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
c_{min}	minimum observed plasma concentration
c_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CL/F	Apparent relative total clearance
CNS	Central Nervous System
DoE	Design of experiments
EC	European Commission
EEG	Electroencephalogram
ESL	Eslicarbazepine acetate
FACL	Oral suspension formulation proposed for commercial use
FC_{1a}	Oral suspension formulation used in the paediatric clinical development programme
FC	800 mg ESL tablet formulations used in the pivotal clinical trials
FK	600 mg ESL tablet formulations used in the pivotal clinical trials
FN	400 mg ESL tablet formulations used in the pivotal clinical trials
FP	Commercial formulation of ESL tablets
HDPE	High Density Polyethylene
HLA	Human leukocyte antigen
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQ	Intelligence Quotient
(m)ITT	(modified) Intent-to-Treat
Ka	Absorption rate constant
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Per protocol
POS	Partial-onset seizures

PRAC	Pharmacovigilance Risk Assessment Committee
RH	Relative Humidity
RSD	Relative Standard Deviation
SAE	Serious Adverse Events
SD	Standard Deviation
SmPC	Summary of Product Characteristics
ss	steady state
SUDEP	Sudden unexplained death in epilepsy
SOC	System organ classes
t_{max}	Time to maximum observed concentration
TEAE	Treatment-emergent adverse events
QD	Quaque Die, once daily
QOL	Quality of life
QRD	Quality Review of Documents
UV	Ultraviolet
V/F	Volume of distribution
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Submission of the dossier

Bial - Portela & Cª, S.A. submitted on 30 June 2015 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
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	II

The MAH proposed grouping of a line extension application to add a new pharmaceutical form (50 mg/ml oral suspension) and a type II variation to add treatment of children aged 2 years and older (adjunctive therapy in patients with partial-onset seizures with or withour secondary generalisation).

Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated and the Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. The application included a revised RMP version 14.0.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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).

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 MAH 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.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 14 December 2006, 21 June 2007 and 19 September 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

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

CHMP Peer reviewer: N/A

- The application was received by the EMA on 30 June 2015.
- The procedure started on 23 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 9 October 2015.
- During the meeting on 3-6 November 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 19 November 2015, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 19 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 21 June 2016.
- The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on 22 June 2016.
- During the PRAC meeting on 4-8 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed by the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 7 September 2016.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the list of of outstanding issues to all CHMP members on 28 September 2016.
- During the meeting on 13 October 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Zebinix on 13 October 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Epilepsy is a heterogeneous and serious brain disorder characterised by the occurrence of unprovoked recurrent seizures due to abnormal, excessive or hypersynchronous neuronal activity. It can be acquired as a result of an

insult to the brain such as trauma, infection, stroke or a tumour, or can result from a genetic mutation in one or more of the ion channel or neurotransmitter genes or proteins that control brain excitability. Partial-onset seizures (POS) are initially confined to a discrete area of the cerebral cortex, but may spread to involve both cerebral hemispheres resulting in secondary generalisation.

2.1.1. Epidemiology

Epilepsy is a common neurological disorder affecting about 50 million people worldwide (Goldenberg, 2010). The lifetime prevalence is 5 to 10 per 1,000 subjects. Epilepsy affects individuals of all ages whereby the incidence is highest in infants and the elderly. Half of the epilepsies begin before the age of 18 years. More than 50% of patients with epilepsy have POS.

2.1.2. Aetiology and pathogenesis

There are different causes for seizures and epilepsy although in about 70% of patients no cause can be identified. Most primary epilepsies have a genetic basis (idiopathic). POS, however, appear mostly to be acquired as a consequence of a focal lesion. Seizures result from abnormal neuronal signalling, including a decrease of inhibitory synaptic activity or enhancement of excitatory neurotransmission.

2.1.3. Clinical presentation and diagnosis

POS may present as simple or complex seizures, depending on whether consciousness is affected. They can manifest as motor, sensory, cognitive, emotional or autonomic symptoms and, in case of secondary generalisation, as absences, tonic, clonic, tonic-clonic, myoclonic or atonic seizures.

Epilepsy is furthermore associated with substantial comorbidities including seizure-related injuries, depression and anxiety associated with high suicide rates and mortality three times the rate expected in the general population, including sudden unexplained death in epilepsy (SUDEP). Epilepsy in children can differ from epilepsy in adults in terms of brain maturation, occurrence of seizure types not seen in adults and childhood epilepsy syndromes. With regards to POS however it is accepted that the clinical expression is similar in adults and adolescents and children down to the age of 4 years (Guideline on the clinical investigation of medicinal products in the treatment of epileptic disorders, Rev.2/Corr., 2010).

The diagnosis involves a physical examination, medical history and an array of tools including electroencephalogram (EEG) for detecting specific patterns of abnormal brain waves as well as imaging.

2.1.4. Management

Anti-epileptic drugs (AEDs) are the mainstay of epilepsy therapy, aiming at eliminating or reducing seizures. The majority of newly diagnosed epilepsy patients become seizure-free with AED treatment including about 60% on a single AED. However, approximately 20-30% are not satisfactorily controlled. This lack of seizure control means that combination therapy is often needed but a sizeable proportion of subjects continue to have seizures despite therapy with more than one AED. Furthermore, many subjects suffer from significant adverse events (AEs).

A number of AEDs are currently used to treat POS including carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. For refractory POS, some additional AEDs including eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and

zonisamide are also used. Not all of these products were approved for use in children at the time of this report and amongst those approved in the paediatric population, different age limits apply.

2.1.5. About the product

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 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.

At the time of receipt of this application, Zebinix was available as immediate release tablets containing 200 mg, 400 mg, 600 mg and 800 mg of ESL. 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 further increased to 1,200 mg once daily.

2.1.6. Type of Application and aspects on development

With this application, the MAH sought to introduce a new pharmaceutical form and strength, an oral suspension (50 mg/ml) intended for use in children. At the same time, the MAH applied for an extension to the indication for adjunctive therapy of POS in children aged 2 years and above. During the course of the procedure, the MAH decided to restrict the age limit to children older than 6 years of age.

The initially recommended posology in children from 2 to 6 years of age was 10 mg/kg/day once daily as starting dose which should be increased to 27.5 mg/kg/day once daily after one or two weeks, to be further increased to 40 mg/kg/day to a maximum of 1,200 mg once daily based on individual response. In children above 6 years of age, the recommended starting dose was 10 mg/kg/day once daily which should be increased to 20 mg/kg/day once daily after one or two weeks. Based on individual response, the dose could be increased to 30 mg/kg/day to a maximum of 1,200 mg once daily.

Scientific advice was sought during the development program on a number of points including clinical aspects and the acceptability of a data package consisting of studies BIA-2093-208 and BIA-2093-305 (hereafter referred to as Study 208 and Study 305, respectively). Further to advice received from the CHMP that additional information was required in order provide a better understanding of the results observed in Study 305 including the pharmacokinetics (PK) in children, the MAH performed population PK and exposure-efficacy analyses based on a population PK model specific to paediatrics as well as a meta-analysis of study 208 and 305 data in the 6-16 years age range.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a multidose oral suspension containing 50 mg/ml of eslicarbazepine acetate as active substance.

Other ingredients are: xanthan gum (E415), macrogol-100 stearate, methyl parahydroxybenzoate (E218), saccharin sodium (E954), flavour tutti-frutti artificial (contains maltodextrin, propylene glycol, natural and

artificial flavouring, and gum acacia (E414)), masking flavour (contains propylene glycol, water and natural and artificial flavouring) and purified water.

The product is available in amber glass bottles with HDPE child resistant closures containing 200 ml oral suspension, inside a cardboard box. Each cardboard box contains a 10 ml propylene graduated oral syringe with 0.2 ml graduations, and a copolymer push-in bottle adapter, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used to manufacture Zebinix 50 mg/ml oral suspension is the same as that employed for the manufacture of the approved Zebinix tablets. As requested by CHMP during the assessment of this line extension, further information concerning the potential genotoxic impurities obtained from the approved manufacturers has been described in sufficient detail.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of this line extension is to introduce a multidose oral suspension for paediatric use containing 50 mg/ml eslicarbazepine acetate to the existing 200 mg, 400 mg, 600 mg and 800 mg Zebinix tablets. The finished product is presented in 200 ml amber glass bottles with HDPE child resistant closures. A 10 ml syringe is also provided in order to administer the prescribed doses (indicated in section 4.2 of SmPC). This new presentation is an off-white to white suspension, easily redispersible by manual shaking for oral administration.

Eslicarbazepine acetate is an anhydrous, non-hygroscopic white to off white crystalline powder, thermostable in solid form and photostable in both solid state and solution. Only one crystalline form (A) was identified through polymorph screening studies.

The active substance has low bulk density and poor wettability. It is very slightly soluble in aqueous solvents (less than 1 mg/ml at pH between 1.2 and 7.4) and, within the gastrointestinal pH range, the active substance is non ionisable. It is a highly permeable compound.

As the active substance has a low aqueous solubility the particle size is reduced by a milling step during its manufacture to provide an increased surface area and consequently improve dissolution. The particle size distribution of the milled active substance is controlled by a multipoint window specification (minimum 95% $\leq$ 100 μm, and minimum 60% between 10 and 80 μm).

Due to the poor aqueous solubility of the active substance, an oral suspension with appropriate physicochemical properties, good chemical stability and with acceptable organoleptic properties was developed for paediatric use. The reduced particle size distribution allows an adequate dispersability of the active substance in the suspension vehicle providing a homogeneous distribution in the suspension.

Three different formulations were developed during pharmaceutical development of the finished product: formula **FC1a**, formula **FACM** and **FACN**, and formula **FACL** (to be marketed).

Formula **FC1a** was used in phase I, II and III clinical trials and stability studies. The excipients used in formula FC1a were chosen from standard oral suspension excipients such as wetting agents, suspending agents, preservatives, flavouring agents and vehicles. The development of formulations **FACM** and **FACN** (for a phase IIa palatability assessment clinical trial) and formulation **FACL** (proposed for marketing) focused on optimising

the flavouring agents, preservatives and other excipients to obtain an acceptable formulation with the desired viscosity and sweetness.

The excipients in formulation **FACL** (proposed for marketing) are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards (except for the flavouring ingredients contained in the favours tutti-frutti artificial and masking flavour, which comply with the requirements of Regulation (EC) 1334/2008). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The compatibility between eslicarbazepine acetate with the excipients selected for the oral suspension formulation was evaluated. It was concluded that the active substance is compatible with the excipients used in the formulation intended for marketing as well as some of the excipients used in the clinical trials formulations.

Comparative in vitro dissolution studies were performed to demonstrate in vitro equivalence between the dissolution curves for formulation FC1a and formulation FACL in three different media (pH 1.2, pH 6.8, pH 4.5). First studies showed that dissolution tests performed at pH 1.2 and pH 6.8 demonstrated in vitro similarity (f_2>50). However, at pH 4.5 the conditions for the calculation of f_2 were not fulfilled as for the FC1a formulation less than 85% of drug was dissolved within 15 minutes. Therefore CHMP requested further data to support the comparability of the dissolution profiles. Additional dissolution studies for different batches (FC1a and FACL) were performed and it was realised that a slow dispensation of the sample in the dissolution vessel created a bottom deposit, hard to dissolve due to the type of hydrodynamic currents formed with the paddle agitations. It was discussed that such phenomenon cannot occur in vivo because of the peristaltic movements in the stomach and the intestine. Decision was to standardize the sample dispensing, not depositing the sample in the bottom of the vessel but half the way from the bottom. The method and analytical conditions were kept unchanged. The dissolution profiles for all batches tested showed dissolution above 85% within 15 min.

The development of the dissolution test method was adequately described. Although sink conditions were not reached it was decided not to use a surfactant in order not to decrease the discriminatory power of the dissolution method. The discriminatory nature of dissolution method has been demonstrated by making small changes in amounts of excipients influencing viscosity and surface tension of the suspension, and small changes to the manufacturing process.

The proposed manufacturing process for eslicarbazepine acetate 50 mg/ml oral suspension involves conventional techniques commonly used for the manufacture of oral suspensions. During development, different aspects of the manufacturing process were studied to identify the critical steps and optimise the process. The addition order of the components was studied to investigate the influence on the suspension properties as well as stirring periods and temperatures. Based on the results obtained, the addition order, stirring times and temperatures were selected.

A manufacturing process scale-up study was performed to investigate the scalability of the proposed process. The results obtained demonstrated that the oral suspension was compliant with all established specifications and no differences were observed between pilot and industrial batches, and therefore the scale-up was successfully completed.

The primary packaging is amber glass bottles with HDPE child resistant closures containing 200 ml oral suspension, inside a cardboard box. Each cardboard box also contains a 10 ml polypropylene graduated oral syringe with 0.2 ml graduations, and a copolymer push-in bottle adapter (PIBA) that, once placed in the bottle, stays in the bottle allowing the container to be closed with the child resistant cap. This avoids the insertion of the syringe in the bottle, preventing any potential contamination of the suspension during dosing. The materials comply with Ph.Eur. and EC requirements. Confirmation of the child-resistant closure compliance with EN ISO

8317 has been provided. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The dosing device complies with council directive 93/42/EEC. CE marking of the oral syringes is confirmed by the declaration of conformity provided.

The 10 ml syringe was tested to measure volumes of the oral suspension between 1 and 16 ml (volumes commonly used in the clinical development and clinical practice) in order to prove the precision and accuracy of the dispensed dose. These parameters were evaluated by determining eslicarbazepine acetate (ESL) and methyl parahydroxybenzoate assay from six measurements at the lowest, highest and intermediate volumes (1, 5, 10 and 16 ml). The volume measurements presented a linear relationship between the measured and dispensed volume. All the acceptance criteria were fulfilled, confirming that the volume device of 10 ml is accurate and precise in the full range of volumes tested, and also supported the selection of the 10 ml device for commercial purposes.

Extraction studies for the push-in bottle adapter (PIBA) to determine the potential for its components to migrate or leach into the finished product when direct contact occurs were also performed. It has been demonstrated by suitably validated methods that the concentration of potential leachables is below 1 ppm and systemic toxicity is not foreseen at such low concentrations.

Compatibility studies of the oral suspension with the dosing device were not performed since the dosing of the oral suspension is performed immediately before dose administration to the patient and contact time is limited.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: dispensing, mixing and volume adjustment, bottle filling and packaging. One manufacturing site is involved. The process is considered to be a standard manufacturing process.

The in-process controls: appearance, fill volume/weight and immediate cap removal torque (bottle filling phase); appearance (labelling phase); and appearance (cartoning phase)) are adequate for this type of manufacturing process.

The critical steps of the manufacture are shown in the table below (Table 1).

Table 1 - Critical steps of the finished product manufacture

Phase	Critical step
Oral suspension preparation	Materials addition order (as per the manufacturing instruction)
	Mixing time (as per the manufacturing instruction)
Bottle Filling	Bottle filling (Fill Volume / Weight controlled in IPC)
	Bottle capping (Immediate Cap Removal Torque controlled in IPC)

The current maximum bulk-hold period studied for eslicarbazepine acetate 50 mg/ml oral suspension is four days, based on the longest period occurred between bulk manufacture and packaging. Total time of the manufacture will not exceed 30 days; therefore no stability studies on bulk product are necessary.

An acceptable process validation scheme has been provided. Process validation will be performed on three consecutive production scale batches before the product is placed on the market. This is considered satisfactory

in accordance with Annex I of the CHMP Guideline on process validation for finished products - information and data to be provided in regulatory submissions.

Product specification

The finished product release specification, includes appropriate tests for this kind of dosage form. It includes appearance (visual), viscosity (Ph. Eur.), uniformity of mass of delivered doses from multidose containers (Ph. Eur.), dissolution (Ph. Eur.), identification (HPLC), assay of eslicarbazepine acetate (HPLC), degradation products (HPLC), assay of methyl parahydroxybenzoate (HPLC) and microbiological attributes (Ph. Eur.).

Methods for pH, specific gravity and enantiomeric purity are not included in specification and sufficient justification for omission of those tests has been provided. Regarding the pH, the results during development showed that the suspension is unstable at pH below 1.5; the decrease of pH is in connection with formation of degradation products (mainly eslicarbazepine and *R*-licarbazepine). This degradation is controlled by the quantification of the degradation products and therefore it was concluded that the test for pH does not provide further information and can be omitted. It was also accepted to omit specific gravity parameter from the specification based on the consistency of the results gathered to date. Since the stability results available showed no relevant changes to the content of *R*-licarbazepine acetate and all results were below the quantification level of 0.1 % (a/a), it was decided not to include this parameter on the proposed specification.

Regarding resuspendability, during manufacturing, the in-process controls assure that the suspension presents adequate characteristics and at the time of release, no settle of the particles is obtained. Based on available batch analysis data, the test for resuspendability is only included in the stability specification and this is considered acceptable.

The analytical methods used have been adequately described and appropriately validated. A forced degradation study was performed to demonstrate selectivity and capability of the assay method to resolve impurities derived from degradation of the oral suspension. Eslicarbazepine acetate oral suspension samples were exposed to light according to ICH Q1B guideline, heat (bottle stored at 80ºC for two days), acid (0.1 M HCl for 5 hours), base (0.1 M NaOH for 5 hours) and oxidation (3% H_2O_2 for 5 hours). The results presented demonstrate the stability indicating nature of the method. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The final specification has been justified based on experience with six batches of the FACL (to be marketed formulation) in accordance with Ph. Eur. requirements and ICH guidelines.

Batch analysis results are provided for batches used in clinical trials and for three production scale batches of the commercial formulation FACL, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data were provided for three production scale batches of finished product stored under long term conditions at 30 ºC ± 2 ºC/65 % ± 5 % RH for 24 months and for up to 6 months under accelerated conditions at 40 ºC ± 2 ºC / 75% RH ± 5 % RH according to the ICH guidelines. The batches of medicinal product were

identical to those proposed for marketing (formulation FACL) and packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, assay, degradation products, assay of methyl parahydroxybenzoate, enantiomeric purity, resuspendability pH, viscosity, specific gravity and microbial purity. The analytical procedures used are the same that for release and are stability indicating.

An additional supportive stability study was performed on one laboratory scale feasibility batch of the commercial formulation (FACL) and packaged in 200 ml glass round amber bottles closed with HDPE white cap (no child resistant) for up to 36 months under long term conditions at 25 ºC ± 2 ºC/60 % ± 5 % RH, and for up to 6 months under accelerated storage conditions at 40 ºC ± 2 °C/75 % ±5 % RH.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

All the results of the stability studies were well within the specification limits. The stability data showed no significant changes or trends in the physicochemical properties of the suspension over 24 months of storage. The finished product is considered to be photostable in the final packaging material and closure system selected for commercial use.

As mentioned under the product specification section, a forced degradation study was performed to demonstrate the stability indicating nature of the analytical method for assay. Briefly, under acidic conditions eslicarbazepine acetate underwent mild degradation whereas complete degradation of API into eslicarbazepine was observed under alkaline conditions. Eslicarbazepine acetate oral suspension was found to be stable in the presence of oxidants, when exposed at 80ºC for two days or under UV/visible radiation for a factor of five in excess to the levels applied in formal ICH studies.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

In-use stability studies for two production scale batches of the finished product packaged in the primary packaging proposed for marketing were conducted at 30 ºC ± 2 ºC / 65 % ± 5% RH for 3 months at the beginning of the shelf life. This study will be repeated at the end of the proposed shelf life for the same batches and using the same protocol. The results of the in-use stability study were also well within the specification and no trends or changes in the product were observed after repeated opening and closing of the bottles. Based on the results, an in-use shelf life of 3 months after first opening of the bottle is considered acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance used to manufacture Zebinix 50 mg/ml oral suspension is the same as that employed for the manufacture of the approved Zebinix tablets.

Information on development, manufacture and control of the 50 mg/ml oral suspension has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

The toxicology studies conducted with ESL in support of the proposed paediatric indication comprise:

- WIL-682001: Toxicity and toxicokinetic study of 28 days repeat doses of ESL in juvenile dogs;
- WIL-682002: A 10-month oral (gavage) toxicity study of ESL in juvenile Beagle dogs with a 2-month recovery period;
- WIL-3123382: A 17-week oral (gavage) toxicity study of ESL in juvenile Beagle dogs with an 8-week recovery period

Studies WIL-682001 and WIL-682002 were conducted in line with the PIP of Zebinix. Study WIL-3123382 was performed after findings of lymphoid depletion and bone marrow hypocellularity in animals found dead or euthanized in extremis in the completed 10-month juvenile dog toxicity study WIL-682002 to further characterize the potential adverse effects of ESL on the immune system as well as tolerability and toxicokinetic profile.

Furthermore, since the initial marketing authorisation a number of pharmacology, genotoxicity and preclinical dependence studies have been completed. In addition, potential Central Nervous System (CNS) effects at high doses of ESL and effects in animal models of neuropathic pain and epilepsy were evaluated. The results of these studies are briefly summarized in the following sections.

2.3.2. Pharmacology

No new non-clinical pharmacology studies and/or tests were conducted in support of this application.

The precise mechanism of action of ESL is still unknown. In vitro electrophysiological studies indicated that both ESL and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

In an attempt to further investigate the mechanism of action and evaluate the effects in animal models of epilepsy and neuropathic pain as well as the potential CNS effects at high doses, a number of primary, secondary and safety pharmacology studies have been conducted and were evaluated since the initial marketing authorisation. The results of these studies did not change the conclusions made during the original marketing authorisation application.

2.3.3. Pharmacokinetics

No new non-clinical pharmacokinetic (PK) studies have been conducted in support of this application.

2.3.4. Toxicology

Repeat-dose toxicity

The toxicology studies conducted with ESL in support the paediatric development initially included a 28 days repeat dose toxicity study in juvenile dogs (0, 25, 100, 200 mg/kg/day) and a 10 months repeated dose toxicity study with a 2 months recovery after oral administration in juvenile beagle dogs (0, 40, 80, 160 mg/kg/day). In both studies, ESL was administered orally (gavage). Furthermore, due to the findings observed in the 10 months study, a 17 week toxicity study with an 8 week recovery period in juvenile beagle dogs has been performed subsequently to characterize the potential adverse effects of ESL on the immune system as well as tolerability following oral (gavage) administration to juvenile Beagle dogs at doses of 0 (control), 10, 40 and 80 mg/kg/day. In all these studies dogs were treated from post-natal day 21. The dog was selected to evaluate the toxicology of ESL in juvenile animals due to the similar metabolite profile to humans.

In juvenile dogs treatment-induced, dose-related clinical signs (e.g. hypoactivity, tremors, convulsions, vocalization, impaired muscle coordination, impaired equilibrium, rigid muscle tone, clear material around mouth, labored respiration, body cool to touch, pale body, thin, dermal atonia, injected sclera of the eye(s), nystagmus, excess salivation, clear and/or white frothy material around mouth, emesis, and/or pale gums) were apparent after ESL-treatment at ≥ 100 mg/kg/day (study WIL-682001) and at ≥ 80 mg/kg/day (study WIL-682002). Changes in blood chemistry parameters (higher serum cholesterol, triglycerides, alkaline phosphatase, and gamma glutamyl transferase levels) with no organ weight or microscopic correlates occurred at dose levels of 40 mg/kg/day and above. Furthermore, at doses of 80 and 160 mg/kg/day, lower bone mineral content, area, and density in the femurs and lumbar vertebrae (L3-L5) were noted. The blood chemistry and bone parameter alterations had resolved by the end of the 56-day non-dosing recovery period.

In the 10-months study, treatment-related unscheduled deaths occurred in the 40, 80 and 160 mg/kg/day groups. In all cases of unscheduled deaths in the 80 and 160 mg/kg/day groups, test-article related clinical observations occurred concomitantly. Histopathological examination identified mild to moderate bone marrow cellularity and mild to marked lymphoid depletion of lymphoid tissues in all unscheduled deaths animals. The No Observed Adverse Effect Level (NOAEL) was 40 mg/kg/day.

In repeated dose toxicity studies in adult dogs, which were part of the initial marketing authorisation application, clinical signs (e.g. vomiting, loose/coloured faeces, salivation, subdued behaviour, prostrate, unsteady gait), a reduction in food consumption and decreases in body weight gain were observed after ESL-treatment. Increases in liver weights and cholesterol were observed in high dose groups of the longer term studies. Extended activated partial thromboplastin time (aPTT) values were observed in nearly all dose groups mainly concerning females. Changes in urinalysis and blood chemistry parameters as well as decreases in organ weights (uterus, ovary, kidney, testis) were only observed in high dose males and females. The NOAEL for adult dogs was 40 mg/kg/day (male and female) in the 12 months adult study.

A finding, not observed in adult dogs, was the bone marrow cellularity and the lymphoid depletion in lymphoid tissues of all unscheduled deaths of animals in the 10 months study in juvenile dogs. Furthermore, pulmonary inflammation with microscopic findings noted was considered the probable cause of morbidity in one of the 40 mg/kg/day group male, and two 160 mg/kg/day group females.

Due to these findings, an additional 17 week toxicity study in juvenile beagle dogs was performed to identify and characterize the risk of AEs of ESL on the immune system of developing organism. In addition to standard toxicology parameters, this study includes the analyses of immune system parameters like peripheral immunophenotyping parameters and corresponding hematological data, T-cell dependent antibody response and immunohistopathology evaluation of immune system organs. Furthermore, bone marrow smears were analyzed and bone densitometry assessments were conducted. In this study, administration of ESL at 10, 40 and 80 mg/kg/day was well tolerated. There were no test article-related effects on survival, body weights, or food consumption. In addition, there were no test article-related alterations in gross necropsy observations, organ weights, bone densitometry assessments, or histopathologic observations. Test article-related clinical observations were limited to slight tremors in male and females at all dose group, which were consistent with the pharmacological effect of the test article and not considered adverse. There were no adverse test article alterations in hematology, serum chemistry or bone marrow cytology. No adverse effects on immune system parameters were observed during this study. The NOAEL was 80 mg/kg/day for both males and females.

Finally, in the 10 months study in juvenile dogs, bone densitometry assessment of femur and lumbar vertebrae (L3-L5) were conducted by dual energy X-ray absorptiometry analysis. Lower bone mineral content, area and density were observed. Bone densitometry assessment has not been performed in adult dogs. However, an association between bone diseases (decreased bone mineral density and disorders of bone metabolism) and antiepileptic drugs, e.g. carbamazepine, has been reported in humans and are included as adverse reaction in the SmPC.

Genotoxicity

In 2 additional *in vitro* genotoxicity studies performed since the renewal of the marketing authorisation of Zebinix in 2014 (studies 788973 and 789013), ESL was found to be non-mutagenic. In another study (789008), ESL was not clastogenic when tested with human peripheral lymphocyte cells *in vitro*. Overall, the weight of evidence from the whole genotoxicity data package suggests that ESL does not pose a genotoxic risk.

Toxicokinetics

Within the repeated dose studies in juvenile dogs, an evaluation of toxicokinetic parameters was performed. Like in adult dogs, oral administration of ESL to juvenile dogs resulted in systemic exposure to ESL and its metabolites, eslicarbazepine and oxcarbazepine. The majority of systemic exposure was accounted for by eslicarbazepine.

Exposure ratios for the main metabolite eslicarbazepine in children in relation to exposure in juvenile dogs were calculated. Area under the curve (AUC) based exposure in juvenile dogs towards eslicarbazepine was found to be consistently lower than in children. Therefore, no safety margins could be established. Similar findings have been previously described for the studies conducted in adult animals.

Dependence

In a non-clinical study in mice (WIL-312349), ESL produced no signs of dependence potential at dose levels of 250 and 400 mg/kg/day over 21 days. Findings of twitches, tremors and wet dog shakes observed in the 600 mg/kg/day dose during the withdrawal period were single occurrences and were of minor importance. In contrast, treatment with the reference compound diazepam produced significant effects during the withdrawal period indicative of physical dependence (abnormal body carriage, aggression, convulsions, stereotype behavior, straub tail, twitches/tremors, body weight loss).

2.3.5. Ecotoxicity / environmental risk assessment

An updated environmental risk assessment (ERA) was provided in support of this application taking into account the proposed new extended target population. The inclusion of a new pharmaceutical form, (50 mg/mL oral suspension) was otherwise not considered to affect environmental exposure.

Epidemiological data of Forsgren et al. (2005) and Giussani et al. (2014) were used to estimate the prevalence of the disease in adults but also in children. Furthermore, based on sales forecast data in relevant EU countries, a market share of 27.27% was calculated. Consequently, the market penetration factor (F_{pen}) was refined by this market share resulting in a value of F_{pen} = 0.001. Based on this, 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, while a risk to sediment organisms cannot be excluded generally, ESL is not expected to pose a risk to the environment, when used according to the approved indication and posology.

2.3.6. Discussion on non-clinical aspects

The CHMP considered the data from the three non-clinical toxicity studies in juvenile dogs provided in support of this application. Two of the three studies have been conducted in accordance with the PIP. The third study was conducted in response to toxicity findings in one of the earlier studies (10 months repeated dose toxicity study) in order to further characterize the potential adverse effects of ESL on the immune system as well as the general tolerability and toxicokinetic profile. The choice of species (dogs) used to evaluate the toxicology of ESL was considered acceptable by the CHMP due to their similar metabolite profile compared to humans.

Based on the findings in the 10 months repeated dose toxicity study, a NOAEL of 40 mg/kg/day was concluded. In the subsequent 17 week study, administration of ESL at 10, 40, and 80 mg/kg/day was well tolerated. There were no test article-related effects indicative of adverse effects on immune system parameters, and, therefore, the NOAEL was considered to be 80 mg/kg/day for both males and females.

Similar to previous studies in adult animals, exposure in juvenile dogs towards ESL was found to be consistently lower compared to children. Therefore, no safety margins could be established.

Most effects seen in juvenile dogs were similar compared to those observed in adult dogs. Findings, not observed in adult dogs, were bone marrow cellularity and lymphoid depletion in lymphoid tissues of all unscheduled dead animals in the 10 months study. Furthermore, pulmonary inflammation was considered the probable cause of morbidity in three animals. These findings may indicate an immunotoxic potential and potential effect on respiratory system development of ESL and/or main metabolites. However, in the subsequent 17-week study no effects on immune system parameters and no pulmonary inflammation were observed and tehrefore it was concluded that the findings of lymphoid depletion and bone marrow hypocellularity in decedents in the 10-months study were more likely to be a result of drug substance aspiration. Literature references also underscore the hypothesis that bone marrow hypocellularity and lymphoid depletion may be associated with pulmonary inflammation.

Measurements of bone densitometry showed a slight dose dependent decrease in femur bone area, bone mineral content and femur length. The MAH argued that after recalculation of bone mineral content (g) to bone area (cm^2) there was no significant difference to the control (vehicle) group. However, even though the bone mineral density parameter (g/cm^2) is use in clinical practice for bone densitometry, change in decreased bone growth can be diminished by recalculation. Moreover, densitometry was performed at post-natal days 141 and

197 in the 17-week study and at post-natal day 329 in the 10 month study, when plasma concentrations of the main metabolites are significantly lowered in comparison to post-natal day 21 and significantly lower in comparison to paediatrics. It remained also questionable why the differences in densitometry were only observed in female dogs as PK parameters did not reveal significant differences between genders. In the 10 month study, there was an indication of dose-dependent decreases in bone mineral content, area and density in all regions of interest in the high dose female group. The decreases were statistically significant at the end of treatment period in bone mineral content and density at the whole femur and distal femur, in bone mineral content and area at the midshaft femur and in bone mineral content at the proximal femur. Similar to the 17-week study, there was no difference in any of the parameters examined at the end of recovery period.

There are reports on an association between AEDs and decrease in bone mineral density and bone metabolism disorders in the published literature indicates. For this reason, section 4.8 of SmPC of Zebinix already includes bone metabolism disorder as an ADR and no further changes to this section were considered necessary by the CHMP. Additional information on the results of the non-clinical studies was agered to be included in SmPC section 5.3, stating that in the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

The CHMP also reviewed additional non-clinical data that had become available since the initial marketing authorisation. The results of these studies did not change the conclusions made during the original marketing authorisation application. No further studies were considered necessary by the CHMP to support 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.

2.3.7. Conclusion on the non-clinical aspects

Subject to the agreed amendments to SmPC section 5.3, the CHMP considered the application acceptable from a non-clinical point of view. Following introduction of the oral suspension and extension of the indication to the paediatric population, ESL is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

The application for the extension of the indication to adjunctive therapy of POS to children aged 2 years and above was supported by data from one Phase 3 (BIA-2093-305) and three Phase 2 (BIA-2093-208, BIA-2093-202 and BIA-2093-212) trials. All studies had previously been submitted and were reviewed by the CHMP, albeit not in the context of a proposal for an extention of the indication.

The MAH furthermore presented results from population PK modeling and exposure-efficacy analyses as well as a meta-analysis of the efficacy data from study 208 and 305.

To support the introduction of the oral suspension (50 mg/mL), the MAH proposed a bridging approach referring to two previously submitted and reviewed Phase 1 bioequivalence studies (BIA-2093-109 and BIA-2093-122) and providing the results from *in vitro* dissolution tests comparing the oral suspension formulation used in the paediatric clinical development programme (FC_{1a}) with the formulation proposed for commercial use (FACL).

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 Phase	Subjects Randomised	Study title	Study Design	Treatment regimen	Key endpoint(s)
BIA-2093-305 Phase 3, completed Oct 2013 (Part II), June 2015 (cut-off date for Asia), Parts IV and V are ongoing in Asia; final study report Apr 2014 (Part I and II) and Feb 2015 (Parts III, IV and V from Europe and part III from Asia)	304 children Age: 2-18 yrs	Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in children aged 2 years to less than 18 years with a one year open label extension phase	**Part I:** 30-34 week, parallel-group, randomised, placebo-controlled study comprising: an 8-week baseline period, a 6-week double-blind titration period, a 12-week double-blind maintenance period, a ≤4-week double-blind tapering-off period, and a 4-week observational follow-up. **Part II:** Optional, 1-year, open-label extension for subjects who completed Part I. **Part III to V:** Optional, open-label extension periods (Parts III and IV: 1-year, Part V: 2-years) for subjects who had completed the previous Study Part.	**Part I:** Daily doses of ESL: 10-30 mg/kg/day QD (maximum 1200 mg/day) *or* placebo **Part II:** Starting dose of 10 mg/kg/day ESL QD that could be titrated up or down at 10 mg/kg/day intervals between 10-30 mg/kg/day (maximum of 800 mg/day and 1200 mg/day, respectively). **Part III to V:** Continued with dose received, could be titrated up or down by 10 mg/kg/day intervals between 10-30 mg/kg/day (maximum of 800 mg/day to 1200 mg/day, respectively).	Co-primary: Responder rate; relative reduction in standardised seizure frequency

Study Phase	Subjects Randomised	Study title	Study Design	Treatment regimen	Key endpoint(s)
BIA-2093-208 Phase 2, completed Part II May 2013, Part III April 2015); final study report in Nov 2013 (Part I and II) and Oct 2015	123 children, Age: 6-16 yrs	Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures including effect on cognitive function of eslicarbazepine acetate (ESL) as adjunctive therapy in children aged 6 years to less than 16 years with a one year open label extension phase	**Part I:** 16-20-week, parallel-group, randomised, placebo-controlled study comprising a 4-week observational baseline period, a 4-week double-blind titration period, an 8-week double-blind maintenance period, and a ≤4-week (dependent on dose) double-blind tapering-off period **Part II:** Optional, 1-year, open-label extension for subjects who had completed Part I. **Part III:** Optional, 2-year, open-label extension for subjects who had completed Part II.	**Part I:** Daily doses of ESL: 10-30 mg/kg/day QD (maximum 1200 mg/day) *or* placebo **Part II:** Starting dose of 10 mg/kg/day ESL QD that could be titrated up or down at 10 mg/kg/day intervals between 10 and 30 mg/kg/day (maximum of 800 mg/day to 1200 mg/day, respectively). **Part III:** Continued with dose received, could be titrated up or down 10 mg/kg/day intervals between 10 and 30 mg/kg/day (maximum of 800 mg/day to 1200 mg/day, respectively).	Primary: Change from baseline in composite Power of Attention measure Key secondary: Relative reduction in seizure frequency; responder rate
BIA-2093-202 (supportive) Phase 2, completed April 2006, final study report in 2008	31 children Age: 2-17 yrs	Open-label, multiple dose study to evaluate pharmacokinetic, safety and tolerability of eslicarbazepine acetate (ESL) for partial onset epilepsy in paediatric patients from 2 years to less than 18 years	Single-centre, open-label, multiple-dose study including a 4- week baseline period, 12-week treatment period, 2-week tapering-off period and 2-week follow-up period	ESL QD in all groups: 5 mg/kg/day in the first 4 weeks, 15 mg/kg/day in Weeks 5–8 and 30 mg/kg/day or 1800 mg/day (whichever was less) in Weeks 9–12. Group I (2-6 yrs): oral suspension 50 mg/mL. Group II (7-11 yrs) and Group III (12-17 yrs): tablets	Primary PK parameters of ESL and metabolites Key secondary Change from baseline in seizure frequency
BIA-2093-212 (supportive) Phase 2, completed Dec 2012, final study report June 2013	38 children, Age: 5-7 yrs	Double-blind study in paediatric epileptic subjects aged from 5 to less than 8 years to compare the subject preference for ESL suspension formulation with alternative flavours	Multicentre, double-blind, randomised, palatability (taste) study	3 different flavours for ESL oral suspension were tasted (not ingested) in a randomised order	Primary: Subject preference of 3 flavours of ESL oral suspension (VAS)

2.4.2. Pharmacokinetics

Oral suspension

In order to support the application for a new oral suspension (50 mg/mL) intended for use in children, the MAH conducted dissolution tests and proposed a bridging approach between the oral suspension formulation intended for commercuial use (FACL), the oral suspension formulation used in the paediatric clinical development programme (FC1a), the tablet formulations used in the pivotal clinical trials (FN, FK and FC) and the commercial formulation of the tablets (FP) as shown in Figure 1.

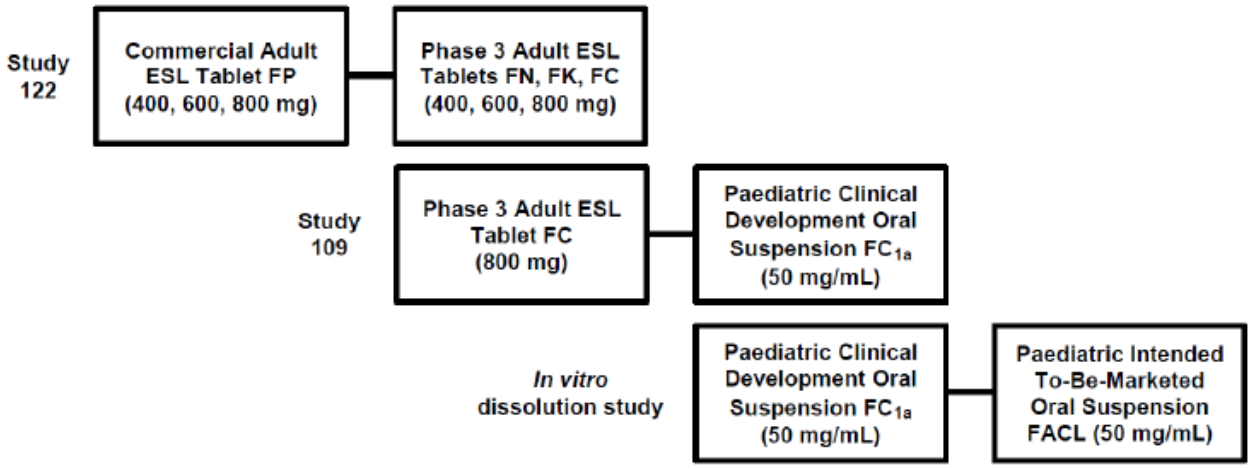


Figure 1 – Bridging scheme for adult tablets and paediatric oral suspension

No *in vivo* study investigating the bioavailability of the FACL formulation had been conducted by the time of this report.

The bridging approach relies on the following findings that had already been reviewed at the time of the initial marketing authorisation application for Zebinix:

- The relative bioavailability of the oral suspension clinical trial FC_{1a} formulation in comparison to the clinical trials tablet FC formulation (800 mg) has been investigated in bioequivalence study BIA-2093-109 (study 109). This was a single centre, open label, randomized, three period, crossover study. The study consisted of three consecutive single-dose treatment periods separated by a washout period of 7 days or more. In each treatment period, the volunteers received a single dose of ESL 800 mg (1x 800 mg tablets; 4x 200 mg tablets; 16 ml of an oral suspension). The study showed bioequivalence of the FC_{1a} oral suspension formulation and the FC 800 mg tablet formulation. Furthermore bioequivalence was shown between FO 200 mg and FC 800 mg tablet formulations. The tablet formulations differed in terms of qualitative and quantitative composition and notably including (FC) or excluding (FO) the excipient sodium lauryl sulphate. Based on the study findings, it could be concluded that neither significant qualitative changes in the formulation nor the dosage form had a relevant effect on the bioavailability of ESL.
- Additionally, since the excipients of the commercial tablet formulation differed from the excipients of the tablet formulations used in the pivotal clinical trials, bioequivalence study BIA-2093-122 was conducted to compare the commercial FP tablet formulation with the clinical trials formulations (400 mg FN, 600 mg FK and 800 mg FC). This study was a single centre, open label, randomized, 2 period, 2 sequence,

crossover study. In summary, bioequivalence was demonstrated and the results indicated no clinical relevant influence of the formulation.

- The effect of food on the bioavailability of the commercial tablet formulation was investigated in study BIA-2093-117. The study showed that bioavailability of an 800 mg oral dose of ESL administered under fed and fasting conditions was similar and bioequivalence criteria were met.

The results of the comparative dissolution profiles of the clinical trial oral suspension formulation FC_{1a} and the to be marketed FACL formulation are summarised in section 2.2. In addition simulations were performed by the MAH using a physiologically based pharmacokinetic (PBPK) model to elucidate the effect of single excipients on the absorption of ESL. The mdoel was built based on PK data from clinical study BIA-2093-202, using patients with age ranging 2-6 years and taking the oral suspension. Prediction PK parameters were generated for formulations with and without sorbitol and were found to be similar thus suggesting that sorbitol in the oral suspension formulation does not impact the PK profile of ESL.

Special populations: Paediatrics

To support the extension of indication to the paediatric population from a clinical pharmacology perspective, the MAH provided data from two studies. The PK of ESL in children was investigated in Study 202, which had already been submitted at the time of the initial marketing authorisation application. PK sampling was furthermore performed in Study 305 and PK data from this study were used alongside the data from Study 202 to develop a population PK model that describes the PK of ESL in children and which was then used in exposure/response analyses of eslicarbazepine, the main active metabolite of ESL, in children.

In both studies, ESL was administered QD as a paediatric oral suspension formulation (FC1a) in subjects aged 2 to 6 years and as an adult tablet formulation (FO, FN, FK, and FC in Study 202; FP in Study 305) in subjects aged >6 years. To assess the effect of age, subjects from Study 202 and 305 were divided into 3 age groups: 2 to 6, 7 to 11, and 12 to 18 years. In Study 202, 11 subjects were in the 2 to 6 years age group, 8 were in the 7 to 11 years age group, and 10 were in the 12 to 18 years age group; in Study 305, 33 subjects were in the 2 to 6 years age group, 52 were in the 7 to 11 years age group, and 51 were in the 12 to 18 years age group.

For details on the study design and methods as well as a summary of the results, see sections 2.5.2.1. (study 305) and 2.5.3. (study 202).

Absorption and distribution

In adults, ESL is extensively converted to eslicarbazepine by hydrolytic first-pass metabolism. Plasma levels of ESL usually remain below the limit of quantification following oral administration. Eslicarbazepine t_{max} is attained at 2 to 3 hours post-dose and steady state plasma concentrations are attained after 4 to 5 days of once daily dosing. Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of the administered ESL dose.

As in adults, ESL was also found in childen to be rapidly and extensively biotransformed to its major active metabolite eslicarbazepine. Following once daily (QD) administration of ESL 5, 15, and 30 mg/kg/day to children aged 2 to 6 years, 7 to 11 years, and 12 to 17 years, maximum plasma concentrations of eslicarbazepine were generally attained between 1 and 3 hours, which is in agreement with the results in adult subjects. T_{max} values were similar across the age groups. While eslicarbazepine c_{max} was generally similar across the age groups following administration of identical ESL doses (in mg/kg), the area under the plasma concentration-time curve

(AUC) decreased with decreasing age due to a faster plasma clearance rate for ESL in younger versus older subjects (see elimination below).

Elimination

Previous studies in adults had furthermore shown that the binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. As in adults, other, minor metabolites in plasma of children are R-licarbazepine and oxcarbazepine.

Dose proportionality and time dependencies

The relationship between the systemic exposure of subjects to eslicarbazepine with increasing doses of ESL in study 202 is presented in following table.

Table 2 - Relationship between the extent of systemic exposure to eslicarbazepine with increasing doses of ESL by age group (Study 202)

Group	Dose (mg/kg/day)	Fold increase in Dose[#]	C_{max} (ng/mL)	Fold increase in C_{max}[#]	AUC_{τ} (ng.h/mL)	Fold increase in AUC_{τ}
Group 1 (2-6 yrs)	5	1.0	6921	1.0	53599	1.0
	15	3.0	16183	2.34	169925	3.17
	30	2.0	29935	1.85	339387	1.99
	Overall[*]	6.0	-	4.33	-	6.33
	DPF[+]	1.0	-	0.72	-	1.05
Group 2 (7-11 yrs)	5	1.0	4820	1.0	51748	1.0
	15	3.0	16395	3.40	206080	3.98
	30	2.0	26890	1.64	378259	1.84
	Overall[*]	6.0	-	5.58	-	7.3
	DPF[+]	1.0	-	0.93	-	1.21
Group 3 (12-17 yrs)	5	1.0	6382	1.0	83691	1.0
	15	3.0	17194	2.69	251638	3.0
	30	2.0	32400	1.90	476183	1.89
	Overall[*]	6.0	-	5.08	-	5.69
	DPF[+]	1.0	-	0.85	-	0.95

[#] Fold increase in dosage or parameters between adjacent dosages
[*] Fold increase in dosage or parameter over the dose range 5 to 30 mg ESL
[+] DPF = Dose proportionality factor = ratio of fold increase in parameter divided by fold increase in dosage

Following the administration of ESL 5 mg/kg/day, AUC from 0 to 24 hours (AUC_{0-24}) was 36% and 41% lower, respectively, in the 2 to 6 years and the 7 to 11 years age groups compared with the 12 to 17 years age group. Following the administration of 15 mg/kg/day, AUC_{0-24} was 33% and 18% lower, respectively, in the 2 to 6 years and the 7 to 11 years age groups compared with the 12 to 17 years age group; and following the administration of 30 mg/kg/day, AUC_{0-24} was 29% and 21% lower, respectively, in the 2 to 6 years and the 7 to 11 years age groups compared with the 12 to 17 years age group.

Following the administration of ESL 5 mg/kg/day, plasma clearance (CL/F, normalized by body weight) was increased by 57% and 69%, respectively, in the 2 to 6 years and 7 to 11 years age groups compared with the

12 to 17 years age group; following the administration of 15 mg/kg/day, plasma clearance was increased by 49% and 21%, respectively, in the 2 to 6 years and 7 to 11 years age groups compared with the 12 to 17 years age group, and following the administration of 30 mg/kg/day, plasma clearance was increased by 47% and 31%, respectively, in the 2 to 6 years and 7 to 11 years age groups compared with the 12 to 17 years age group.

Furthermore, C_{24h} (C_{min}) increased with age and was nearly two-fold lower in the youngest age group compared to the adolescents (12-18 years) in study 202.

In all paediatric age groups, both c_{max} and AUC from 0 to 24 hours post-dose at steady state ($AUC_{0-24,ss}$) were dose proportional. The MAH concluded a dose-proportional increase in exposure to eslicarbazepine with increasing doses of ESL in the three age groups.

Pharmacokinetic interaction studies

No studies have been conducted in children.

Population PK model

The MAH presented a population PK analysis performed on pooled data from two studies 202 and 305 (Part I). The analysis was based on a population PK model specfically developed for children and adolescents. The population PK model was built using the data of study 202 including 29 patients and 664 observations (i.e., 664 eslicarbazepine concentration data points). Thereafter, 362 observations from 136 subjects in Study 305 were used as a validation dataset. Finally, the model was updated according to the pooled dataset.

Population PK parameters were estimated by non-linear mixed-effect modelling using NONMEM version 7.2. A 1-compartment model with first-order absorption and elimination fitted the Study 202 data adequately. The model was parameterised in terms of the absorption rate constant (K_a), CL/F, and volume of distribution (V/F). Exponential models were used to describe the inter-individual variability on all parameters, and a proportional model was considered to be the best model for proportional error. The influence of age group was considered a structural covariate in the base model.

In order to confirm the predictive performance of the population PK model, upon request of the CHMP, the MAH provided prediction corrected Visual Predictive Checks (pcVPCs) (Bergstrand et al., 2011), which showed that median concentrations were generally well predicted, only variability is at some time points slightly overpredicted and 95% percentiles slightly overpredicted at some time points in age group 3 and 5% percentile underpredicted at late time. Overall, the pcVPCs did not indicate any major model misspecification.

In terms of covariates, only the influence of weight on CL/F and V/F was found to be significant. In the final model, CL/F was affected by body weight, and the effect of body weight differed between the youngest age group (2 to 6 years) and the 2 older age groups (7 to 11 and 12 to 18 years). This was accounted for in the final model. V/F had moderate variability and is affected by body weight independently of the age group. K_a, which reflects both absorption rate of the parent drug and its biotransformation into eslicarbazepine, was smaller in the youngest age group (2 to 6 years) compared with the 2 older age groups (7 to 11 and 12 to 18 years). The MAH considered that this was most likely related to faster drug metabolism in younger subjects (2 to 6 years age group).

For each age group and dosing regimen scenario, 1000 simulations of PK parameters (CL/F, V/F, and K_a) were obtained. Derived PK parameters ($AUC_{0-24,ss}$, minimum observed plasma concentration at steady state [$c_{min,ss}$], and $c_{max,ss}$) were then calculated.

Exposure parameters were further assessed using an ESL reference dose of 20 mg/kg/day QD. This was the dose selected as target dose in Study 305 because effective ESL doses in adult Phase 3 studies were 800 and 1200 mg QD, and a dose of 1200 mg QD (which is also the maximum approved maintenance dose for adults) corresponds to 20 mg/kg/day assuming an average adult body weight of 60 kg. It is also proposed by the MAH to be administered in clinical practice as maintenance dose for children aged >6 years.

Based on the calculated PK parameters at this dose, systemic exposure was found to be comparable between the 2 older age groups (7 to 11 and 12 to 18 years). However, both median $AUC_{0-24,ss}$ and $c_{max,ss}$ were reduced in subjects aged 2 to 6 years relative to the 2 older age groups. Following further simulations in the youngest age group, a minimum daily dose of ESL 27.5 mg/kg/day QD was found to be necessary for the 2 to 6 years age group to match the eslicarbazepine exposure achieved with ESL 20 mg/kg/day QD in the older paediatric age groups.

Upon request of the CHMP, the MAH presented further simulations for AUC, minimum and average concentration at steady state ($AUC_{0-24,ss}$, $c_{av,min}$ and $c_{av,ss}$) for the age groups >6 years in comparison to adult values. Simulations were run using the updated POPPK adult model, including data from study BIA-2093-304. The results indicate comparable simulated exposure to eslicarbazepine based on all three values for the adult dose of 800 mg and the paediatric dose of 20 mg/kg/day as well as for the adult dose of 1200 mg and the paediatric dose of 30 mg/kg/day, respectively.

Palatability

Study BIA-2093-212 was a double-blind phase 2 study in paediatric epileptic subjects aged from 5 to less than 8 years to compare preferences for ELS oral suspension formulation with alternative flavours. The study has previously been submitted and was assessed by the CHMP although at the time of the assessment no oral suspension of Zebinix had been approved for the EU market.

Three different flavours (tutti-frutti, grape, and banana) were tested. After tasting and spitting out each sample, the child was asked to rate the taste on a 10 cm visual analogue scale (VAS) incorporating a facial hedonic scale. A comparison of mean VAS scores showed that there was no statistically significant difference between the 3 tested flavours. Nevertheless, the mean VAS score for tutti-frutti was higher (7.1) than for grape (5.8) or banana (5.8). Tutti-frutti was furthermore more frequently considered the best flavour (39.5) compared with grape (31.6%) and banana (28.9%). In addition, tutti-frutti was less frequently considered the worst flavour (18.4%) compared with grape (44.7%) and banana (36.8%).

2.4.3. Pharmacodynamics

Now new pharmacodynamic studies for the paediatric population have been conducted.

Subsequent to the development of the paediatric population PK model, the relationship between exposure and efficacy was simulated using data from Study 305 (see section 2.5.2.). The relative reduction of standardised seizure frequence observed in Study 305 in the intent-to-treat (ITT) population was plotted against the mean daily dose of ESL (21 mg/kg/day) for the total ITT population and the estimated exposure to eslicarbazepine (283 mg.h/L [283000 ng·h/mL]) for the total ITT population (Figure 3). Both plots indicate an approximately 20% reduction in standardised seizure frequence with versus without ESL treatment.

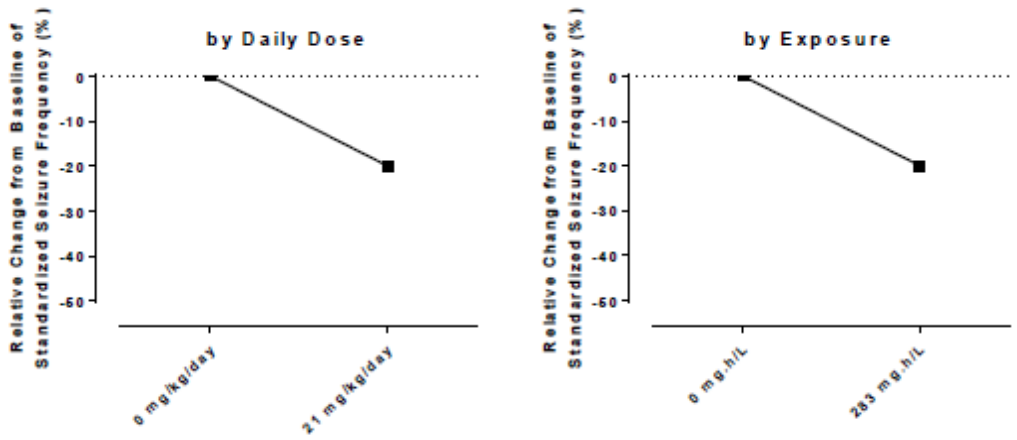


Figure 2 - Relationship between ESL dose or eslicarbazepine exposure and relative reduction in standardised seizure frequency

2.4.4. Discussion on clinical pharmacology

Oral suspension

Within the paediatric development programme for ESL, the MAH developed an oral suspension (50 mg/mL ESL) in order to account for the special needs of paediatric patients, which was in line with the paediatric investigation plan. The application for the oral suspension was not supported by *in vivo* bioequivalence study data. Rather, the MAH proposed a bridging approach relying on studies previously conducted and assessed, which showed comparable bioavailability of (i) the commercial tablet formulation and the clinical trial tablet formulation and (ii) the clinical trial tablet formulation and the clinical trial oral suspension formulation FC_{1a}. To support similarity of the clinical trial oral suspension FC_{1a} formulation and the to be marketed oral suspension FACL formulation, comparative dissolution profiles were generated. The data showed that the *in vitro* dissolution profiles of the two oral suspension formulations were similar. Additional simulations furthermore suggested that the presence or absence of sorbitol in the oral suspension formulation had no impact on the PK of ESL.

Overall, the available PK data indicated that ESL has a low potential for formulation effects. Differences in the composition of the formulations, the change of dosage form or concomitant administration of food had no major effect on bioavailability. Therefore, extrapolation of the conclusions on efficacy and safety obtained from studies with clinical trial formulations (suspension and tablets) was considered justified as intrinsic properties of ESL appear to have a low potential for formulation effects. While no problem was foreseen in patients being started on Zebinix, as the optimum dose for this product is titrated individually, uncertainties remained in relation to the interchangeability of the tablets and the oral suspension in patients who would like to switch formulations during ongoing treatment. In response to this concern, the MAH presented an analysis of exposure, efficacy and safety findings for 23 patients in study 305, who had switched from the oral suspension (clinical trials formulation) to tablets (commercial formulation) during Part II (open-label extension) of the study. While the analyses showed no relevant differences in exposure and seizure frequency for the treatment periods 'time to switch' and 'time after switch', the CHMP considered that full interchangeability could not be confirmed in the absence of comparative biovailability data with the commercial oral suspension and tablet formulations. The CHMP therefore was of the view that section 4.2 of the SmPC should be updated to include a statement that switching between tablets and oral suspension should be done with caution.

The CHMP acknowledged the MAH's efforts to determine the most acceptable taste of the liquid formulation to

children in a palatability study. Although the results have not shown any particular taste preference, this is not a critical issue, since the purpose of flavouring is to increase patient comfort and compliance with therapy. Lack of statistical significance for one particular taste is acceptable and the choice of tutti-frutti flavour for the commercial formulation was justified.

Paediatric population

In order to support the application for an extension of the indication to the paediatric population, the MAH conducted one PK study in the paediatric population (study 202) in order to characterize PK parameters of ESL in children. This study has previously been submitted and was reviewed by the CHMP in the context of the initial marketing authorisation application. PK data were also collected in the context of the pivotal phase 3 trial 305. In addition, results of a population PK analysis have been presented.

Based on these data it can be concluded that ESL behaves similarly in children and adults in terms of biotransformation to the active metabolite eslicarbazepine and attained t_{max} values. However, exposure data have not been consistent across age groups and dose ranges. Generally, exposure (AUC) was lower in younger children (2-6 years) compared to older children (7-18 years). The MAH argued that this could have been caused by quicker clearance in younger children. However, uncertainties remained as dropout rates in study 202 were high (26 of 35 patients completed al treatment periods) and there were some serious adverse events leading to discontinuation, the reason of which could be unpredictable exposure values.

Population PK results showed that body weight had an effect on volume of distribution and clearance. In the youngest age group (2-6 years), age seemingly also played a role independently of weight with regards to clearance of ESL. Furthermore, the absorption rate constant was smaller in the youngest age group compared to the older age groups (7-11 and 12-17 years). According to simulations based on the population PK model, a minimum daily dose of 27.5 mg/kg/day is necessary in the age goup of 2-6 year olds to match the exposure achieved with 20 mg/kg/day in older children. Doses for 2-6 year old children to match exposure with 30 mg/kg/day in older children would obviously exceed this dose, which was the highest explored dose in the clinical trials. It was not possible to formally evaluate if this difference could be ascribed to faster drug metabolism in the younger patients or better drug absorption with the oral suspension (which was given to patients aged 2-6 years in the clinical trials) as compared to tablets (given to patients older than 6 years in the studies). The MAH also stated that impact of a faster drug elimination through a specific pathway is dependent on the degree of maturation of the drug eliminating organs. Therefore the effect of genetic polymorphisms, as well as hepatic or renal impairment on the pharmacokinetics within the 2-6 age group, could be different from the effect in adults. Moreover, since the liver may well not be fully developed within the 2-6 age group, data on interactions may be more difficult to estimate by extrapolation. In light of the uncertainties arising from the PK differences between the youngest age group and the poor efficacy results in this age group observed in the pivotal trial 305 (see section 2.5. for details), the MAH decided during the course of this procedure to no longer pursue an extension of the indication to children from 2 years of age, but to limit the age range to children older than 6 years. This was agreed by the CHMP.

With regards to children aged >6 years, in order to determine the appropriate dose range, the MAH simulated exposures based on $AUC_{0\text{-}24,ss}$, $c_{av,min}$ and $c_{av,ss}$ values, using an adult and a paediatric population PK model. The simulations showed similar results for the approved adult maintenance doses and the proposed paediatric maintenance doses, i.e. comparable exposure values were achieved in adults and children following an adult dose of 800 mg/day and a paediatric dose of 20 mg/kg/day and following an adult dose of 1200 mg/day and a paediatric dose of 30 mg/kg/day, respectively. The CHMP considered that these results supported the posology recommendation, namely that after administration of a starting dose of 10 mg/kg/day, the dose should be increased up to 30 mg/kg/day based on individual response.

2.4.5. Conclusions on clinical pharmacology

From a biopharmaceutical point of view the CHMP considered the application for the new 50 mg/ml oral suspension acceptable. However, as full interchangeability of the oral suspension and the tablets could not be confirmed in the absence of suitable bioavailability data, caution is advised when switching pharmceutical forms. The CHMP recommended for the MAH to conduct a relative bioavailability study comparing the commercial formulations of the tablets and the oral suspension.

With regards to proposed extended target population, the CHMP was of the view that the avilable PK data as supplemented by simulations from population PK modelling were adequate to support an extension of the indication of Zebinix to patients aged more than 6 years based on a recommended maintenance dose of 20 and 30 mg/kg/day.

2.5. Clinical efficacy

Within the ESL paediatric development programme, 3 clinical trials were conducted, including one Phase 3 study (Study 305) and 2 Phase 2 studies (Study 208 and 202), that were relevant to the evaluation of efficacy in the proposed extended indication of adjunctive therapy in children and adolescents with POS with or without secondary generalisation. The MAH furthermore presented a meta-analysis of the key Phase 2 and 3 studies 208 and 305.

All studies results (except for the meta-analysis) had previously been reviewed by CHMP. A summary of the study design, methods and main results is provided in this section.

2.5.1. Dose response study(ies)

No dose response studies have been conducted.

The choice of the ESL dose in the pivotal confimatory phase 3 study 305 was based on the findings from the phase 3 add-on trials in the adult population and studies in children, whereby the effective doses were 800 and 1200 mg/day and 1200 mg/day corresponds to an average of 20 mg/kg/day assuming a body weight of 60 kg. Furthermore, PK studies had shown a faster clearance of the active ESL metabolite eslicarbazepine in younger children.

Based on these findings, the MAH set the target dose at 20 mg/kg/day with the possibility to increase the dose to 30 mg/kg/day in case of unsatisfactory therapeutic response up to a maximum daily dose of 1200 mg.

2.5.2. Main study(ies)

Both of the two main studies (305 and 208) were designed in several parts. This section summarises the results of the respective double-blind placebo-controlled phase. Open-label extension data are summarised in section 2.5.3.

2.5.2.1. Study 305 (Part I)

Study BIA-2093-305: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial.

Methods

In this study, efficacy and safety of ESL was evaluated compared to placebo (part I) in children aged 2 to less than 18 years with a diagnosis of POS who were refractory to treatment with 1 to 2 AEDs with 4 subsequent one year open-label extension phases (study parts II-V).

Study Participants

Main inclusion criteria:

- Children 2 to 16 years of age; as per Global Amendment 4 (16 Sep 2010): children 2 to 18 years of age.
- Diagnosis of epilepsy for at least 6 months prior to enrolment.
- At least 4 POS in the last month prior to enrolment despite stable therapy with adequate dosage of 1 or 2 AEDs.
- At least 4 POS during each 4-week interval of the 8-week baseline period and stable dose regimen of AEDs during the 8-week baseline period.
- Previous treatment with ≥3 AEDs, in their maximum tolerated doses, for at least 1 month, without seizure control (Amendment 1 Portugal, 30 Aug 2007 and Global Amendment 1, 20 Dec 2007).
- Current treatment with 1 or 2 AEDs (any AED except oxcarbazepine); if present, vagus nerve stimulation is considered an AED (Global Amendment 1, 20 Dec 2007).

Main exclusion criteria:

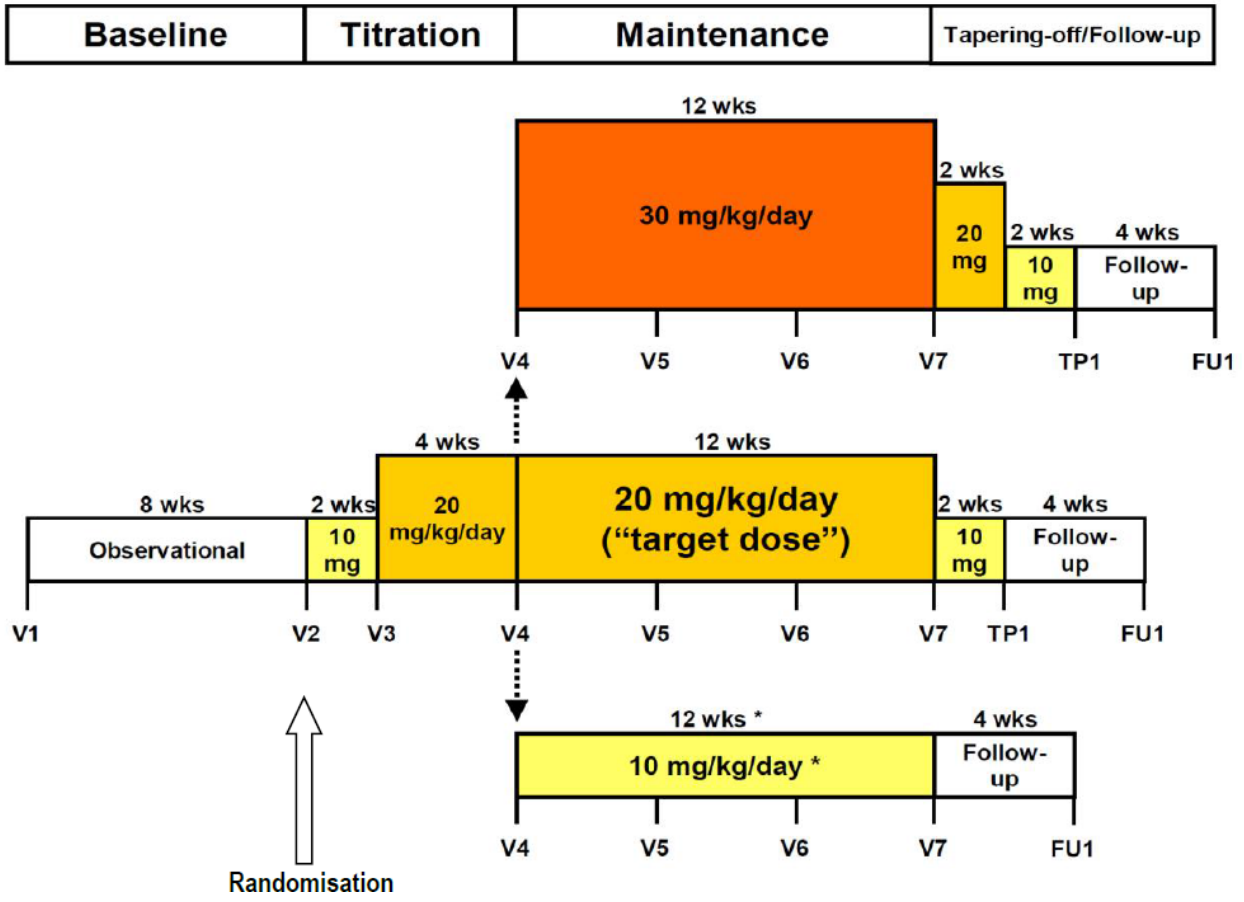
- Primarily generalised seizures.
- Baseline seizure frequency substantially different from usual seizure frequency.
- Known progressive neurological disorders (progressive brain disease, epilepsy secondary to progressive cerebral lesion).
- History of status epilepticus within the 3 months prior to enrolment.
- Seizures of non-epileptic origin (e.g. metabolic, neoplastic, or related to active infection).
- Epileptic syndromes (Lennox-Gastaut syndrome, West syndrome).
- Major psychiatric disorders.
- Previous treatment in any study with ESL.
- Safety: Known second or third degree atrioventricular (AV) block (Global Amendment 4, 16 Sep 2010); history of hypersensitivity to the investigational products or to drugs with similar chemical structures; impaired renal function, as shown by pre-defined abdnormal laboratory findings; any other clinically significant abnormal laboratory findings at screening; pregnancy or breast-feeding; patients from Asian countries only: positive for the human leukocyte antigen B*1502 (HLA-B*1502).

Treatments

Part I consisted of the following treatment periods:

- An observational 8-week baseline period.

- A 6-week titration period.
- A 12-week maintenance period.
- A tapering-off period (2-week steps of down-titration by 10 mg/kg/day).
- A 4-week observational follow-up period.



FU = follow-up visit TP = tapering-off visit; V = visit; wks = weeks.
* Only for patients down-titrated from 20 mg/kg/day due to intolerable AEs.
Note: Patients were randomised to ESL or placebo (Visit 2). Dosages refer to ESL or placebo.
Visits TP1 and FU1 also had to be performed for patients who discontinued early from the study treatment.

Figure 3 - Dose Schedule and Study Design, Part I

Figure 3 provides an overview of the study design and treatment schedule.

The recommended dose ("target dose") of double-blind study treatment was 20 mg/kg/day (up to a maximum of 1200 mg/day). The study treatment (ESL or placebo) was administered as follows:

Titration period:

- For the first 2 weeks (from Visit 2 to 3), the study treatment was given at a dose of 10 mg/kg/day (up to a maximum of 800 mg/day). If the patient reported an intolerable adverse event (AE) during these 2 weeks on 10 mg/kg/day (maximum 800 mg/day), the patient was withdrawn from the study.
- If no intolerable AEs occurred during these 2 weeks, the patient was up-titrated at Visit 3 to the target dose of 20 mg/kg/day (maximum 1200 mg/day) and received this dose for 4 weeks. If intolerable AEs

occurred during the 4 weeks on 20 mg/kg/day (maximum 1200 mg/day) from Visit 3 to 4, the dose was down-titrated to 10 mg/kg/day (maximum 800 mg/day). Visit 4 was performed at the time of down-titration.

Maintenance period:

- If at Visit 4, after 4 weeks on 20 mg/kg/day (maximum 1200 mg/day), the tolerability of study treatment and therapeutic response were considered acceptable, the patient continued treatment at 20 mg/kg/day (maximum 1200 mg/day) for a further 12 weeks (from Visit 4 to 7).
- If at Visit 4, the tolerability of study treatment was considered acceptable but the therapeutic response was judged unsatisfactory, the patient was up-titrated to 30 mg/kg/day (maximum of 1200 mg/day) and received this dose for 12 weeks (until Visit 7).
- Patients who were down-titrated to 10 mg/kg/day (maximum 800 mg/day) during the titration period received this dose for 12 weeks during the maintenance period (from Visit 4 to 7).
- If intolerable AEs occurred during the maintenance period, the patient was down-titrated to the previous dose for the remainder of the maintenance period or discontinued. Down-titration was allowed only once. If a patient experienced intolerable AEs after downtitration, the patient was discontinued from the study treatment and withdrawn

Study treatments were provided as an oral suspension or as white oblong tablets. Patients aged 2–6 years (stratum I) received the oral suspension of 50 mg/mL ESL or matching placebo suspension. The dose was rounded to the nearest 50 mg unit. Patients aged 7–18 years (stratum II and III) received tablets of 200 mg strength of ESL or matching placebo tablets. The dose was rounded to the nearest 100 mg unit. Tablets were scored and half tablets were used for dosage adjustment, if necessary.

Objectives

The primary objective of the study was to assess the efficacy of ESL as an adjunctive therapy in children and adolescents with refractory POS.

The secondary objectives of the study were to assess:

- The safety and tolerability of ESL as an adjunctive therapy in children and adolescents with refractory POS.
- The proportion of seizure-free patients and of patients with more than 75% reduction in seizure frequency.
- The frequency of patients with exacerbations.
- The duration of seizures and severity of seizures (using the Hague seizure severity scale).
- The potential for rebound effects and withdrawal phenomena.
- The potential for interactions between ESL and concomitant AEDs.
- The seizure frequency by seizure type.
- The maintenance of the therapeutic effect of ESL during long-term treatment in Part II, Part III, Part IV, and Part V of the study.

Outcomes/endpoints

Two primary efficacy variables were defined:

1. Responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

2. Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

The primary efficacy variables were based on the seizure frequency as recorded in patient diaries. The occurrence and duration of seizures and any symptoms (i.e. warning symptoms, loss of consciousness, falls, injuries, other) were recorded. For each patient and period, the mean daily seizure frequency was calculated (i.e. the total number of seizures divided by the patient's individual number of observational days within the respective study period). Seizure frequency was standardised to a 4-week interval within each study period (i.e. the mean daily seizure frequency was multiplied by 28 days). Patients with missing seizure information were set to non-responders.

The **secondary efficacy variables** were:

- Standardised seizure frequency per period of the baseline, titration, maintenance, and tapering-off periods.
- Relative change in seizure frequency from the baseline period to the 12-week maintenance period (≥25%; >–50% to <25%; ≥–75% to ≤–50%; <–75%).
- Proportion of patients who are seizure-free during the maintenance period.
- Standardised seizure frequency by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other) during the maintenance period. Seizures with missing seizure type information were considered as unclassified for the analysis.
- Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, ≥5 min, unknown.
- Seizure severity assessed with the 13-item Hague seizure severity scale.
- Number of days with seizures (standardised to 4-week time period).
- Treatment retention time, defined as the time to first occurrence of one of the following during the titration or maintenance period: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
- Seizure exacerbations during tapering-off or follow-up period.

Sample size

The sample size calculation was based on the 2 primary efficacy variables. With regards to the responder rate, a sample size of 216 patients (108 per treatment arm) was estimated to have a power of 80% to detect a difference of 18% between active and placebo arms (as observed in other, previous studies with AEDs) with a 5% type I error. As for the relative reduction in seizure frequency, a 25% difference in the relative reduction in seizure frequency between treatments was considered a clinically relevant difference and corresponded to the

average relative difference to placebo in other AED add-on studies [Glauser, 2006]. It was estimated that a sample size of 216 patients (108 per treatment arm) was sufficient to detect such difference with an Standard Deviation (SD) of 40% and a conditional power of at least 8% (the condition was that the test on the responder rate was already significant) while ensuring a type I error of 5%. Considering a drop-out rate of approximately 15%, approximately 252 patients were to be randomised (126 per treatment group).

Randomisation

At the end of the baseline period , eligible patients were randomised in a 1:1 ratio (stratified by age: stratum I: 2-6 years; stratum II: 7-11 years; stratum III: 12-18 years) to receive ESL or placebo in addition to concomitant therapy with 1 or 2 AEDs. A centralised randomisation procedure was applied using block randomisation based on a randomisation list created by means of computerised techniques.

Blinding (masking)

Part I of the study was conducted under double-blind conditions. Blinding was ensured by the use of matching placebo tablets or suspension. The randomisation list and the allocation to treatment groups were unknown to the investigator, the Sponsor, or any other person involved in the conduct of the study until study completion, except in case of an emergency.

Statistical methods

- Analysis sets

On 04 Jun 2009, the distribution of oral suspension of study medication was stopped due to stability issues resulting in dark spots visible in the vials. Patients in stratum I (2-6 years of age) who received the investigational medicial product as oral suspension had to stop intake immediately and any unused study medication had to be returned. Since it could not be ruled out that the issues with the oral suspension formulation used in stratum I patients had an impact on the efficacy and safety results, the data of stratum I patients randomised before the recall were presented separately. After closure of the Part I database and unblinding, it was found that the issue with the oral suspension only affected the placebo formulation; thus, the impact of this issue on efficacy was expected to be none. Based on this, the following analysis sets were defined:

Enrolled set: all patients for whom informed consent was available.

Randomised set: all patients randomised to study medication irrespective of whether they actually received study medication.

Intention-to-treat (ITT) set: all randomised patients treated with at least 1 dose of study medication after randomisation, and with at least 1 post-baseline seizure frequency assessment, excluding those stratum I patients who were randomised before the recall of the oral suspension (see below).

ITT set (stratum I patients randomised before oral suspension recall): all randomised stratum I patients treated with at least 1 dose of study medication before the recall, and with at least 1 postbaseline seizure frequency assessment.

Modified ITT (mITT) set: all randomised patients treated with at least 1 dose of study medication after randomisation, and with at least 1 post-baseline seizure frequency assessment, including also those stratum I patients who were randomised before the recall, i.e. both ITT sets combined.

Safety set: all patients who received at least 1 dose of double-blind study treatment excluding those stratum I patients who were randomised before the recall.

Safety set (stratum I patients randomised before oral suspension recall): All stratum I patients who received at least 1 dose of double-blind study treatment before the IMP recall.

Combined safety set: All patients who received at least 1 dose of double-blind study treatment, i.e. safety set and safety set (stratum I patients randomised before recall) combined.

Per protocol (PP) set: all patients of the ITT set who had a double-blind treatment duration of at least 11 weeks in the maintenance period and who were without any major protocol deviations.

- Analysis of efficacy

Continuous data were summarised using descriptive statistics, i.e. number of patients, mean, standard deviation (SD), minimum, median, and maximum. Categorical variables were summarised using frequency counts and percentages. All statistical tests were 2-sided at an alpha level of 0.05.

The first primary null hypothesis was that the responder rate (patients with a reduction in seizure frequency of ≥50%) for patients treated with ESL during the maintenance period is not different from that for patients treated with placebo. The second primary null hypothesis was that the relative change in standardised seizure frequency for patients treated with ESL during the maintenance period is not different fromthat for patients treated with placebo. The second primary null hypothesis was only tested if the first primary null hypothesis had been rejected following the hierarchical testing strategy. The primary hypothesis was tested 2-sided at a significance level of 0.05. The hierarchical testing procedure controlled for type I error inflation due to multiple testing, and therefore an adjustment of the significance level was not necessary.

In the primary efficacy analysis, the responder rate during the 12-week maintenance period was analysed by a Cochran-Mantel-Haenszel (CMH) test with age groups (I: 2-6 years; II: 7-11 years; III: 12-16 [18] years) as the stratification factor. Responder rates, odds ratios, their respective confidence intervals (CIs), the Breslow-Day test for homogeneity of the odds ratios, and p-values were presented. The relative change in standardised seizure frequency was compared among the treatment groups using an analysis of covariance (ANCOVA) that modelled the relative change in standardised seizure frequency during the maintenance period as a function of stratum group (I: 2-6 years; II:7-11 years; III: 12-16 [18] years), baseline seizure frequency, and treatment.

To check the robustness of the primary efficacy results, the primary efficacy analysis was also performed using the randomised (excluding the patients in stratum I randomised before the recall) and PP sets. Furthermore, the primary analysis was repeated using age group instead of stratum group as factor for the ITT set. Additionally, the primary analyses were repeated for the mITT set, where patients in stratum I treated before the recall were considered to belong to a separate stratum (stratum I before recall).

Secondary efficacy variables were analysed descriptively. Additional statistical tests conducted for Part I of the study were of exploratory nature only and included the following:

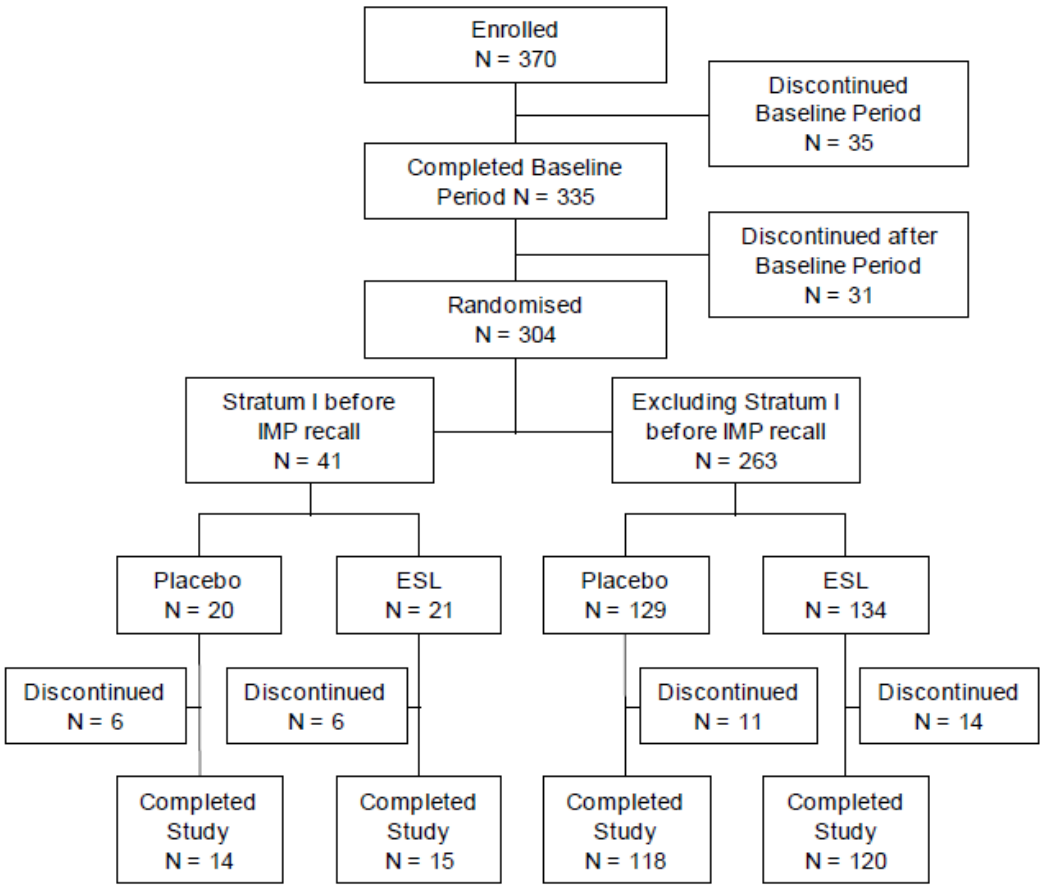
The responder rate was also analysed using a logistic regression models that assessed the effect of region, age/age category, and number of concomitant AEDs. The relative change in SSF was also compared between treatment groups using ANCOVAs that included additional factors for region, age, and number of concomitant AEDs. Results on the primary efficacy variables were also provided by study period and by seizure type.

The standardised number of days with seizures was analysed by a CMH test. The distribution of the treatment retention time was descriptively summarised using Kaplan-Meier estimates and pairwise log rank tests stratified by region were carried out to compare the treatment groups.

Results

Participant flow

A total of 370 patients were enrolled into the study and started the baseline period (Figure 4). Of these, 66 patients discontinued the study either during or after the baseline period. Therefore, 304 patients were randomised.



IMP = Investigational Medicinal Product

Figure 4 - Patient disposition flow chart

In the safety set, 238 patients (90.5%) completed the study. A similar number of patients withdrew from the study in both treatment groups (14 patients [10.4%] in the ESL group and 11 patients [8.5%] in the placebo group). The most common reason for withdrawal was patient's (or patient's legally authorised representative's) own request (5 patients [3.7%] in the ESL and 5 patients [3.9%] in the placebo group). During the titration period, 6 (4.5%) ESL patients and 5 (3.9%) placebo patients discontinued the study, and during the maintenance period, 8 (6.3%) ESL patients and 4 (3.2%) placebo patients discontinued the study.

Recruitment

The first patient was enrolled by 07 December 2007 and the date of last patient completing the double-blind treatment period (Part I) was 20 Aug 2012.

Conduct of the study

At the time of reporting there were 5 global and 8 national amendments to the original protocol (dated 15 Jun 2007). The impact of these amendments on the inclusion/exclusion criteria is described in the methods section.

Global Amendment 1 (20 Dec 2007) intended to harmonise the requests from different Ethics Committees and/or Regulatory Authorities.

Global Amendment 2 and 3 (29 Apr 2009 and 17 May 2010) introduced two 1-year, open-label extension (Part III and IV) to allow patients who participated in this study to continue receiving ESL.

Global Amendment 4 (16 Sep 2010) was mainly due to a recall of the oral suspension formulation of the study medications (50 mg/mL ESL or placebo) used in the age group of 2-to-6-year-old children (stratum I). The oral suspension was recalled due to stability issues (see methods section for impact on analysis sets).

Global Amendment 5 (12 May 2011) introduced a 2-year, open-label extension (Part V) amongst a number of other changes.

Baseline data

The demographics and baseline disease chracteristics are described in Table 2 and Table 3.

Table 3 – Demographics (safety set)

Parameter	Statistic/Category	Placebo (N=129)	ESL (N=134)
Age (years)	Mean (SD)	9.5 (3.85)	9.9 (4.22)
	Median (range)	10.0 (2.0, 17.0)	10.0 (2.0, 18.0)
Age group	2-6 years	31 (24.0)	31 (23.1)
	7-11 years	53 (41.1)	51 (38.1)
	12-18 years	45 (34.9)	52 (38.8)
Sex, n (%)	Male	62 (48.1)	64 (47.8)
	Female	67 (51.9)	70 (52.2)
Race, n (%)	Caucasian	117 (90.7)	123 (91.8)
	African (black)	1 (0.8)	0
	Asian	10 (7.8)	11 (8.2)
	Other	1 (0.8)	0
Region, n (%)	Eastern Europe [a]	81 (62.8)	76 (56.7)
	Western and Northern Europe [b]	9 (7.0)	11 (8.2)
	Southern Europe [c]	29 (22.5)	37 (27.6)
	Asia [d]	10 (7.8)	10 (7.5)

ESL = eslicarbazepine acetate; N = number of patients in the safety set; n = number of patients with data; SD = standard deviation.
[a] Hungary, Poland, Romania, Russia, Slovakia, and the Ukraine.
[b] Austria, France, Germany, and the United Kingdom.
[c] Bosnia and Herzegovina, Croatia, Italy, Portugal, Serbia, and Spain.
[d] Malaysia, Philippines, and Taiwan.

There were no relevant differences between treatment groups regarding disease aetiology and family history. In the safety set, the mean age at onset of epilepsy was 3.0 years in the ESL group and 2.9 years in the placebo group. Median durations of epilepsy in the ESL group were 38.3 months in age group 1, 84.9 months in age group 2, and 119.2 months in age group 3; corresponding median durations of epilepsy in the placebo group were 43.9, 78.2, and 110.8 months, respectively. The most frequently reported aetiologies of the disease were congenital/hereditary (20.9% ESL, 20.2% placebo) and idiopathic (14.2% ESL, 16.3% placebo). The aetiology was reported as unknown for 24.6% of ESL patients and for 30.2% of placebo patients. At least 90% of patients in either group had no disease history in their families.

Table 3 shows that the median standardised number of seizures during the baseline period was lower in the ESL group than in the placebo group.

Table 4 - Standardised seizure frequency during the baseline period (safety set)

Parameter	Placebo (N=129)			ESL (N=134)		
	n (%)	Mean (SD)	Median (range)	n (%)	Mean (SD)	Median (range)
Any seizure	129 (100)	62.0 (186.19)	17.0 (3.9, 1972.5)	134 (100)	36.6 (72.47)	11.5 (3.7, 605.8)
Simple partial	71 (55.0)	66.0 (198.42)	14.0 (0.5, 1564.5)	65 (48.5)	34.3 (82.38)	8.0 (0.4, 605.8)
Complex partial	78 (60.5)	25.3 (53.94)	6.2 (0.5, 405.0)	84 (62.7)	19.3 (40.06)	6.0 (0.4, 233.0)
Partial evolving to secondarily generalised	63 (48.8)	14.8 (26.86)	6.0 (0.5, 150.0)	60 (44.8)	12.6 (31.19)	4.0 (0.4, 193.0)
Unclassified	18 (14.0)	4.1 (4.15)	2.6 (0.4, 13.8)	17 (12.7)	10.3 (23.93)	0.9 (0.5, 99.4)
Other	10 (7.8)	32.7 (51.11)	3.7 (0.5, 141.5)	11 (8.2)	11.8 (19.00)	4.9 (0.5, 62.5)

ESL = eslicarbazepine acetate; N = number of patients in the safety set; n = number of patients with respective seizure type; SD = standard deviation

As required per protocol, all patients took at least 1 concomitant AED during Part I. There were no relevant differences between treatment groups in the use of concomitant AEDs during the study. At the end of the baseline period, the majority of patients took 2 concomitant AEDs (73.1% of ESL patients, 72.9% of placebo patients). The remaining patients either took 1 (15.7% and 19.4%, respectively) or 3 concomitant AEDs (11.2% and 7.8%, respectively). The most common AEDs taken at the end of the baseline period (reported for ≥20% of patients) were valproic acid, lamotrigine, carbamazepine, topiramate, and levetiracetam, with frequencies of patients taking these AEDs varying between 22.4% and 31.0%. During the titration and/or maintenance period, 24 patients (17.9%) in the ESL group and 19 patients (14.7%) in the placebo group changed their AED medication.

Numbers analysed

Table 4 provides an overview of the number of patients per analysis set. Overall, 37 patients (27.6%) in the ESL group and 28 patients (21.7%) in the placebo group had a major protocol violation or a treatment duration in the maintenance period of <11 weeks. These patients were therefore excluded from the PP set, which consequently included 97 patients (72.4% of the safety set) in the ESL group and 101 (78.3%) in the placebo group.

Table 5 – Analysis Sets (Study 305 Part I)

Analysis set	Number (%) of patients		
	Placebo	ESL	Overall
Enrolled set	-	-	370
Overall (including stratum I before IMP recall)			
Randomised set	149 (100.0)	155 (100.0)	304 (100.0)
Combined safety set	149 (100.0)	155 (100.0)	304 (100.0)
Modified ITT set	149 (100.0)	155 (100.0)	304 (100.0)
Excluding stratum I before IMP recall			
Safety set	129 (100.0)	134 (100.0)	263 (100.0)
Stratum I (after IMP recall)	33 (25.6)	31 (23.1)	64 (24.3)
Stratum II	51 (39.5)	52 (38.8)	103 (39.2)
Stratum III	45 (34.9)	51 (38.1)	96 (36.5)
ITT set	129 (100.0)	134 (100.0)	263 (100.0)
Per-protocol set	101 (78.3)	97 (72.4)	198 (75.3)
Stratum I before IMP recall			
Safety set (stratum I before IMP recall)	20 (100.0)	21 (100.0)	41 (100.0)
ITT set (stratum I before IMP recall)	20 (100.0)	21 (100.0)	41 (100.0)

ESL = eslicarbazepine acetate; IMP = investigational medicinal product; ITT = intention-to-treat

Outcomes and estimation

For both **primary efficacy variables**, the response rate and the relative change in the standardised seizure frequency during the maintenance period, no statistically significant difference between ESL and placebo was found (see Table 5, Table 6 and Table 7). Forty-one patients (30.6%) in the ESL group compared to 40 patients (31.0%) in the placebo group were responders, resulting in a non-significant odds ratio of 0.97 (95% confidence interval [CI]: 0.57, 1.63; p=0.9017). The least square (LS) mean relative change in the standardised seizure frequency was higher in the ESL group (-18.1%) than in the placebo group (-8.6%), resulting in a LS mean difference of 9.5% (95% CI: -6.71, 25.77; p=0.2490). A trend in favour of ESL compared to placebo was also observed when the standardised seizure frequency was based on the titration + maintenance period instead of the maintenance period.

Results from pre-planned sensitivity analyses and additional post-hoc analysis methods were consistent with the primary analysis results. There were also no relevant between-treatment differences concerning seizure type or other study periods.

Table 6 – 50% responders during maintenance and titration + maintenance periods (ITT)

Statistic	Placebo (N=129)	ESL (N=134)
Maintenance period (primary endpoint) [a]		
Number (%) of responders	40 (31.0)	41 (30.6)
CMH test [b]		
Odds ratio vs. placebo	0.97	
95% CI	[0.57; 1.63]	
p-value for comparison vs. placebo	0.9017	
Homogeneity of odds p-value [c]	0.2001	
Titration + maintenance period (post-hoc) [d]		
Number (%) of responders	29 (22.5)	34 (25.4)
CMH test [b]		
Odds ratio vs. placebo	1.15	
95% CI	[0.65; 2.04]	
p-value for comparison vs. placebo	0.6218	
Homogeneity of odds p-value [c]	0.3631	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ESL = eslicarbazepine acetate; ITT = intention-to-treat; N = number of patients in ITT set.
[a] Missing seizure information during maintenance period was imputed with the maximum of the standardised seizure frequency during baseline and titration period.
[b] Stratified by stratum group.
[c] From Breslow-Day test; significance indicating heterogeneity.
[d] Missing seizure information during titration + maintenance period was imputed with the standardised seizure frequency during the baseline period.

Table 7 - Standardised seizure frequency – descriptive statistics (ITT set)

			Relative change from baseline period (%)	
Study Period	**Placebo (N=129)**	**ESL (N=134)**	**Placebo (N=129)**	**ESL (N=134)**
Baseline period				
Mean (SD)	62.0 (186.19)	36.6 (72.47)	-	-
Median (min, max)	17.0 (3.9, 1972.5)	11.5 (3.7, 605.8)	-	-
Maintenance period [a]				
Mean (SD)	46.7 (80.99)	30.4 (62.76)	-9.6 (70.15)	-19.2 (64.10)
Median (min, max)	11.2 (0.0, 425.7)	7.2 (0.0, 492.1)	-25.9 (-100.0, 264.5)	-26.1 (-100.0, 366.7)
Titration + maintenance period (post-hoc) [b]				
Mean (SD)	47.8 (78.34)	30.6 (64.03)	-6.1 (64.59)	-17.7 (57.03)
Median (min, max)	11.8 (0.0, 405.9)	7.5 (0.0, 536.6)	-18.8 (-100.0, 219.8)	-24.0 (-100.0, 366.7)

ESL = eslicarbazepine acetate; ITT = intention-to-treat; max = maximum; min = minimum; N = number of patients in ITT set; SD = standard deviation.
[a] Missing seizure information during the maintenance period was imputed with the maximum of the standardised seizure frequency during baseline and titration period.
[b] Missing seizure information during the titration + maintenance period was imputed with the standardised seizure frequency during the baseline period.

Table 8 - Relative reduction in standardised seizure frequency during maintenance and titration + maintenance periods (ITT set)

	Placebo (N=129)		ESL (N=134)
Maintenance period			
LS mean (SE) relative reduction (%)	-8.6 (5.93)		-18.1 (5.84)
95% CI	[-20.24, 3.12]		[-29.58, -6.60]
ESL vs. Placebo [a]			
LS mean (SE)		9.5 (8.25)	
95% CI		[-6.71, 25.77]	
p-value		0.2490	
Titration + maintenance period (post-hoc)			
LS mean (SE) relative reduction (%)	-4.7 (5.35)		-16.4 (5.26)
95% CI	[-15.25, 5.81]		[-26.78, -6.06]
ESL vs. Placebo [a]			
LS mean (SE)		11.7 (7.43)	
95% CI		[-2.95, 26.33]	
p-value		0.1169	

CI = confidence interval; ESL = eslicarbazepine acetate; ITT = intention-to-treat; LS = least square; N = number of patients in ITT set; SE = standard error.
[a] ANCOVA model with treatment and stratum group as fixed effects and baseline seizure frequency as a covariate. P-values for stratum group: 0.0320 (maintenance), 0.0092 (titration + maintenance); p-value for baseline seizure frequency: 0.3068 (maintenance), 0.1876 (titration + maintenance).

Secondary efficacy findings were as follows:

- Frequency of seizure-free patients during the maintenance period was 3.9% ESL versus 2.4% placebo and during the tapering-off period: 9.2% ESL versus 12.6% placebo.
- Frequency of patients with seizure reduction of at least 75% during the maintenance period was 15.6% ESL versus 12.9% placebo ad during the tapering-off period 13.4% ESL versus 20.3% placebo.
- Frequency of patients with exacerbation (increase of ≥25%) during the maintenance period was 13.3% ESL versus 13.7% placebo and during the tapering-off period 14.3% ESL versus 15.3% placebo.
- The majority (>80%) of seizures during the maintenance period lasted <1 minute in both treatment groups. The proportion of seizures with a duration of <30 seconds was lower in the ESL group (46.7%) than in the placebo group (68.0%), while for seizures with a duration of 30-<60 seconds the proportion was higher for ESL (35.6%) than for placebo (20.9%).
- During the study, small mean increases in the total score of the Hague seizure severity scale were seen in both treatment groups, slightly larger in the ESL group (mean increases between 1.4 and 2.5) than in the placebo group (mean increases between 0.5 and 1.6).
- In each study period, the mean standardised number of days with seizures was slightly lower in the ESL group than in the placebo group. In both treatment groups, the mean standardised number of days with

seizures was highest during the baseline period (12.2 days ESL; 13.9 days placebo) and lowest during the maintenance period (9.3 days ESL; 11.9 days placebo).

- There was no interaction between the number of concomitant AEDs or concomitant carbamazepine and treatment in the ANCOVA of the relative change in standardised seizure frequency.
- No rebound effects were observed. The standardised seizure frequency during tapering-off and follow-up periods increased in relation to the maintenance period, but not to a value greater than that observed at baseline. Furthermore, the increase in standardised seizure frequency during tapering-off and follow-up periods in relation to baseline was similar in both treatment groups.

Ancillary analyses

Additional analyses defined after database lock and unblinding of the data were performed for the subgroup of patients by strata (stratum I: age 2-6 years, stratum II: age 7-11 years and stratum III: 12-18 years). Initial analyses compared stratum I patients with combined data for stratum II+III. Patients in strata II and III received study drug orally as tablets while the younger patients of stratum I received study drug as oral suspension.

In stratum I, 5/31 patients (16.1%) in the ESL group compared to 11/33 patients (33.3%) in the placebo group were responders (odds ratio: 0.38; p=0.1122). In the titration + maintenance period, responder rates were 12.9% and 21.2%, respectively (odds ratio: 0.55; p=0.3786). In stratum II+III, 36/103 patients (35.0%) in the ESL group compared to 29/96 (30.2%) in the placebo group were responders, resulting in a non-significant odds ratio of 1.24 (95% CI: 0.68, 2.25; p=0.4759). In the titration + maintenance period, 30/103 patients (29.1%) in the ESL group compared to 22/96 (22.9%) in the placebo group were responders, resulting in an odds ratio of 1.38 (95% CI: 0.73, 2.62; p=0.3191). Separate analyses for the two older age strata, showed that in stratum II, 15/51 patients (29.4%) in the ESL group compared to 16/52 (30.8%) in the placebo group were responders, resulting in a non-significant odds ratio of 1.07 (95% CI: 0.46, 2.48; p=0.8806). In stratum III, 20/51 (39.2%) in the ESL group compared to 14/45 patients (31.1%) in the placebo group were responders (odds ratio: 0.70, 95% CI: 0.30, 1.63; p=0.4074).

Additional analyses for stratum II+III were carried out on the standardised 4-week seizure frequency. In this group, the LS mean relative change in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period was higher in the ESL group (-24.4%, SE: 5.91, 95% CI: -36.09, -12.79) than in the placebo group (-10.5%, SE: 6.12, 95% CI: -22.58, 1.56); however, the LS mean difference of 13.9% was not statistically significant (95% CI: -2.89, 30.74; p=0.1040). When based on the titration + maintenance period, the LS mean difference between ESL and placebo was slightly larger than that based on the maintenance period, resulting in a statistically significant difference of 16.2 (95% CI: -1.08, 31.32, p=0.0359). When stratum II and III were analysed separately, LS mean relative change in standardised seizure frequency from the baseline to maintenance period was -14.8 and -0.7% for the ESL and the placebo group in stratum II and -34.9 and -20.9% for the ESL and the placebo group in stratum III. The difference was not statistically significant in either group.

Further post-hoc analyses by age strata and dose received during the maintenance period were carried out to elucidate the efficacy findings in the younger age group and the relation to the ESL dose received (see Table 9 and Table 10).

Table 9 – Number of responders – 30 and 20 mg/kg/day in maintenance (ITT set)

Statistic	30 mg/kg/day		20 mg/kg/day	
	Placebo	ESL	Placebo	ESL
Including Stratum I				
Total number of patients	51 (100%)	47 (100%)	50 (100%)	47 (100%)
Number (%) of responders	17 (33.3%)	16 (34.0%)	18 (36.0%)	19 (40.4%)
Chi test [a]				
Odds ratio vs. placebo	1.09		1.26	
95% CI	[0.48; 2.47]		[0.55; 2.86]	
p-value	0.8390		0.5851	
Excluding Stratum I				
Total number of patients	36 (100%)	29 (100%)	42 (100%)	42 (100%)
Number (%) of responders	11 (30.6%)	14 (48.3%)	14 (33.3%)	17 (40.5%)
Chi test [a]				
Odds ratio vs. placebo	2.11		0.72	
95% CI	[0.77; 5.82]		[0.30; 1.75]	
p-value	0.1514		0.4665	

[a] Chi—test not stratified by age stratum

Table 10 - Relative reduction in standardised seizure frequency during maintenance – 30 and 20 mg/kg/day in maintenance (ITT set)

Statistic	30 mg/kg/day		20 mg/kg/day	
	Placebo	ESL	Placebo	ESL
Including Stratum I				
No. of patients	51	47	50	47
% LS mean (SE) RR	-8.3 (8.30)	-30.3 (8.57)	-32.8 (8.22)	-34.9 (8.74)
95% CI	[-24.77, 8.18]	[-47.36, -13.33]	[-49.08, -16.45]	[-52.23, -17.50]
ESL vs. Placebo				
LS mean (SE)	22.1 (11.78)		2.1 (11.09)	
95% CI	[-1.34, 45.44]		[-19.92, 24.12]	
p-value	0.0644		0.8501	
Excluding Stratum I				
No. of patients	36	29	42	42
% LS mean (SE) RR	-5.2 (10.83)	-37.2 (11.93)	-22.2 (8.84)	-24.5 (8.77)
95% CI	[-26.87, 16.44]	[-61.02, -13.29]	[-39.78, -4.57]	[-41.97, -7.07]
ESL vs. Placebo				
LS mean (SE)	31.9 (15.82)		2.3 (12.43)	
95% CI	[0.31, 63.57]		[-22.39, 27.08]	
p-value	0.0478		0.8509	

ANCOVA model with treatment as fixed effect and baseline seizure frequency as a covariate; LS Mean = Least Square Mean, SE = Standard Error; RR = Relative reduction

While the target dose in study 305 was 20 mg/kg/day, further titration up to 30 mg/kg/day was allowed. A total of 39% patients [47 and 51 patients in the ESL and the placebo group, respectively) were uptitrated to the maximum possible dose (30 mg/kg/day for ESL). Of these 16 (34.0%) and 17 (33.3%) in the ESL and the placebo group, respectively, were responders (odds ratio: 1.09; p=0.8390). In stratum I, more patients in the placebo group than in the ESL group were responders at a dose of 30 mg/kg/day [6/15 (40.0%) versus 2/18 (11.0%)]. When excluding stratum I patients from the analysis, 14/29 (48.3%) and 11/36 (30.6%) of patients in the ESL and placebo group, respectively, were responders (odds ratio: 2.11; p=0.1514). With regards to

relative reduction in seizure frequency during the maintenance phase, patients receiving the 30 mg/kg/day dose had a LS mean reduction (SE) of -30.3% (8.57) compared to -8.3 (8.30) in the corresponding placebo group. The LS mean difference was 22.1 (p=0.0644). When excluding stratum I, the difference became statistically significant (LS mean difference: 31.9, p=0.0478).

For both responder rate and reduction in standardised seizure frequency, the difference between ESL and placebo was much greater for the 30 mg/kg/day than for the 20 mg/kg/day doses in Strata II+III. The difference in relative reduction in standardised seizure frequency between 30 mg/kg/day ESL and placebo was ~30%. In contrast, the difference to placebo for the 20 mg/kg/day ESL dose was ~2%.

2.5.2.2. Study 208 (Part I)

Study BIA-2093-208: Effects of eslicarbazepine acetate (BIA 2-093) on cognitive function in children with partial onset seizures: an add-on, double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial.

Methods

In this study the effects on cognition as well as efficacy and saftey of ESL as adjunctive therapy in children aged 6 to 16 years old with refractory POS despite receiving 1 to 2 AEDs were investigated. The study was designed in 3 parts: an initial double-blind placebo-controlled trial (Part I), a 1-year open-label extension (Part II), and an additional 2-year open-label extension (Part III), which was introduced as an amendment to the protocol.

Study Participants

Main inclusion criteria:

- Aged 6 to 16 years, inclusive.
- Documented diagnosis of epilepsy for at least 12 months prior to screening.
- At least two POS during the 4 weeks prior to screening despite treatment with 1 to 2 AEDs in a stable dose regimen.
- At least two POS during the 4-week baseline period prior to randomization (documented in a diary).
- Current treatment with 1 to 2 AEDs (any except oxcarbazepine); the dose regimen ahd to be stable during the 4-week baseline period.
- An intelligence quotient of at least 70 as assessed within the 1 year prior to screening.

Main exclusion criteria:

- Only simple POS with no motor symptomatology.
- Primarily generalized seizures.
- Known rapidly progressive neurological disorders (progressive brain disease; epilepsy secondary to progressive cerebral lesion).
- Occurrence of seizures too close together to count accurately.
- History of status epilepticus or cluster seizures (i.e., 3 or more seizures within 30 minutes) within the 3 months prior to screening.

- Seizures of non-epileptic origin or within the last 2 years seizures of psychogenic origin.
- Epilepstic syndromes (Lennox-Gastaut syndrome, West syndrome).
- Major psychiatric disorders or history of schizophrenia or suicide attempt.
- Documented and established diagnosis of Attention-Deficit Hyperactivity Disorder currently treated with stimulants or history of other diseases adversely affecting cognitive abilities.
- Treatment with oxcarbazepine, occasional use of benzodiazepine for any reason other than epilepsy, on ketogenic diet or receiving Vagus Nerve Stimulation.
- Safety: Known hypersensitivity to carboxamide derivatives (oxcarbazepine or carbamazepine); uncontrolled cardiac, renal, hepatic, endocrine, gastrointestinal (GI), metabolic, hematological or oncology disorder; second or third-degree atrioventricular blockade; relevant clinical laboratory abnormalities; estimated creatinine clearance < 60 mL/min; pregnancy or nursing.
- Treatment with ESL in any previous study.

Treatments

Part I consisted of the following treatment periods:

- An 4-week observational baseline period.
- A 12-week double-blind period: 4-week up-titration and 8-week maintenance
- A tapering-off period (2-week steps of down-titration by 10 mg/kg/day).
- A 4-week observational follow-up period.

Patients received either placebo QD or ESL QD. Patients in the ESL group received during the 4-week titration period, ESL 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks, to a maximum dose of 1200 mg/day. During the 8-week maintenance period, patients received ESL 30 mg/kg/day to a maximum dose of 1200 mg/day. If intolerable AEs occurred, patients were either to be down-titrated to the previous dose (only one down-titration step was allowed) or withdrawn from the study.

ESL was provided as 200 mg tablets. The dose was rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary.

Objectives

The primary study objective was to evaluate the effects of ESL on cognition in comparison with placebo as adjunctive therapy in children aged 6 to 16 years old with refractory POS.

The secondary objectives of this study were to evaluate in comparison with placebo the safety and tolerability of ESL, efficacy of ESL as adjunctive therapy in children with refractory partial epilepsy, the effect of ESL on global cognitive skills, social competence and quality of life (QOL). Furthermore, to evaluate the effects of long-term treatment with ESL as adjunctive therapy on global cognitive skills, social competence and QOL as well as safety, tolerability, and sustainability of the therapeutic effect of ESL.

Outcomes / endpoints

The primary endpoint was change from baseline to the end of the Part I in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

Secondary endpoints in Part I were:

- Relative reduction from baseline in standardised (4-week) seizure frequency over the evaluation period.
- Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period to the 8-week maintenance period (responders).
- Proportion of seizure-free patients (100% seizure reduction) over the 8-week maintenance period.
- Proportion of patients with a 25% or greater exacerbation in seizure frequency versus baseline.

Patients (or parents/legal representatives) were instructed to keep a seizure diary and to record all seizures by date, time of occurrence, and seizure type throughout the study.

Neurocognitive Endpoints in Part I were, from the Cognitive Drug Research neurocognitive test battery, change from baseline to the end of the Part I in the score of Continuity of Attention, Quality of working memory, Quality of episodic secondary memory (children aged ≥ 9 years only), Word recognition (children aged ≥ 9 years only), Picture recognition (children aged < 9 years only) and Speed of memory.

Global Cognitive, Social Competence and Quality of Life Endpoints in Part I were change from baseline to the end of Part I in the number of correct answers on the Raven's Standard Progressive Matrices test, competence summary score from the Child Behaviour Checklist, physical and psychosocial functioning summary score from the Child Health Questionnaire.

Sample size

Assuming a SD of 202.3 for the Power of Attention score, a non-inferiority limit of 121 ms and a one-tailed test at the 0.025 significance level, a total of 102 patients in the Cognitive PP population would provide 80% power to reject the null hypothesis that the mean increase from baseline Power of Attention was at least 121 ms smaller in the placebo group than in the ESL group, versus the alternative hypothesis that any advantage in the placebo group was less than the inferiority limit. Allowing for premature discontinuations and/or major protocol violations (and hence exclusion from the Cognitive PP population), a total of 117 patients were to be randomized (39 patients in the placebo group and 78 patients in the ESL group).

Randomisation

At the end of this baseline period, patients who met the selection criteria were randomly assigned to one of the two treatment groups in a 1:2 ratio. A centralized randomization procedure based on a randomiztion code prepared by means of computerized techniques was used. Randomization was stratified by age (6 to 11 years and 12 to 16 years).

Blinding (masking)

The study was conducted under souble-blind conditions. Thus, neither the investigator nor the patientknew the identity of the study treatment being administered. Tablets used in the two study groups were identical in appearance.

Statistical methods

The following analysis populations were defined for this study:

- Safety population: all randomized patients who received at least one dose of study treatment after randomization.
- Modified Cognitive ITT population: all randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline assessment of cognition.
- Modified Efficacy ITT population: all randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment.
- Cognitive PP population: all patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not important protocol deviations with respect to the primary cognitive endpoint.
- Efficacy PP population: all patients in the Modified Efficacy ITT population who completed the 8-week maintenance period and were not important protocol deviations with respect to the secondary efficacy endpoints.

For the primary analysis, the change from baseline to the end of the double-blind period in Power of Attention score, was compared between the treatment groups using ANCOVA. This analysis was performed for all patients and for each age group separately. In the analysis in all patients, the ANCOVA model included treatment and country as fixed effects and baseline Power of Attention score, age and sex as covariates. In the analyses in each age group, the model included treatment and country as fixed effects and baseline Power of Attention score and sex as covariates. The analyses of the primary endpoint were performed for both the Modified Cognitive ITT and Cognitive PP populations.

Non-inferiority of ESL versus placebo was assessed by comparing the 95% CI's upper bound of the difference of the least square means for the change from baseline between treatment groups with 121 milliseconds (ms). If the upper bound was greater than 121 ms, then the null hypothesis that the change from baseline in the Power of Attention score in ESL group is at least 121 ms inferior than the placebo group was rejected.

Additional exploratory covariate analyses were also performed for the primary endpoint using separate ANCOVA models in all patients. The models included treatment as the main effect and baseline score, age and sex as covariates. Additional baseline covariates, including, age at onset of epilepsy, duration of epilepsy, number of concomitant AEDs at baseline and baseline IQ, were included together with their interactions with treatment.

The majority of secondary analyses weree also conducted using ANCOVA.

All efficacy analyses were performed for the Modified Efficacy ITT population and the Efficacy PP population. For responder analyses, the difference between treatment groups was determinded using a CMH test for ordinal data.

Results

Participant flow

Table 11 – Patient Disposition Study 208 (Part I)

Disposition	Placebo n (%)	ESL n (%)	Total n (%)
Randomized	40 (100.0)	83 (100.0)	123 (100.0)
6-11 years	18 (45.0)	36 (43.4)	54 (43.9)
12-16 years	22 (55.0)	47 (56.6)	69 (56.1)
Entered Maintenance Period	40 (100.0)	76 (91.6)	116 (94.3)
Completed the DB Period	37 (92.5)	75 (90.4)	112 (91.1)
Prematurely Discontinued from the DB Period	3 (7.5)	8 (9.6)	11 (8.9)
Primary Reason for Discontinuation from DB Period[a]			
Request of Patient/Caregiver/Parent	1 (2.5)	2 (2.4)	3 (2.4)
AE(s) (serious or non-serious)	0	3 (3.6)	3 (2.4)
Intolerable AEs at the 10mg/kg/day Dose	0	2 (2.4)	2 (1.6)
Non-Compliance of Patient	1 (2.5)	1 (1.2)	2 (1.6)
Other	1 (2.5)	0	1 (0.8)

Abbreviations: AE = adverse event; DB = double-blind; ESL = eslicarbazepine acetate.
[a] Reasons for premature discontinuation from the DB period include patients who discontinued from either the titration or maintenance periods. Note: Percentages were calculated based on the total number of randomized patients

Recruitment

First patient first visit: 10 August 2010. Last patient last visit (Part I): 21 March 2012.

Conduct of the study

There were a total of three protocol amendments, none of which raised major concerns.

Baseline data

The treatment groups were balanced for age, sex, and race. The mean age was 11.7 years, with similar distributions between age categories (43.9% of patients were 6 to 11 years of age and 56.1% were 12 to 16 years of age). In both treatment groups, the percentage of male patients (65.0% placebo; 56.6% ESL) was higher than female patients (35.0% placebo; 43.4% ESL). Caucasian was the predominant race (122/123 patients, 99.2%). Baseline height, weight, and body mass index (BMI) as wells as head circumference and IQ scores were balanced between the placebo and ESL groups; mean height (151.1 to 150.5 cm), weight (48.7 to 47.7 kg), BMI (20.80 to 20.24 kg/m2), head circumference (53.6 to 54.0 cm), and IQ (89.1 to 87.9).

The number of AEDs being taken at baseline was similar between the two treatment groups. The majority of patients were taking ≤ 2 AEDs at baseline; 51.2% of patients were taking 1 AED and 44.7% of patients were taking 2 AEDs. AEDs used by at least 15% of patients in either treatment group were valproate (60.0% and 47.0%); carbamazepine (30.0% and 31.3%); topiramate (22.5% and 24.1%); and lamotrigine (10.0% and 16.9%) in the placebo and ESL groups, respectively.

The most common seizure types during the 28 days prior to screening were complex partial in both treatment groups (69.9%). More patients in the placebo group had complex partial seizures (80.0%) while more patients in the ESL group had partial evolving to secondary generalized type seizures (34.9%). No patients had

unclassifiable or other seizure types. The median (minimum, maximum) seizure frequency during the 28 days prior to screening was 4.5 (2, 345) in the placebo group and 5.0 (2, 140) in the ESL group.

Numbers analysed

Overall, few patients had important protocol deviations and the majority occurred in the ESL group. For both of the ITT populations, the most frequently occurring important protocol deviation was 'lack of compliance with study drug and/or the seizure diary'.

Table 12 –Analysis Populations (Study 208)

Data Analysis Set	Placebo n (%)	ESL n (%)	Total n (%)
Randomized	40 (100.0)	83 (100.0)	123 (100.0)
6-11 years	18 (45.0)	36 (43.4)	54 (43.9)
12-16 years	22 (55.0)	47 (56.6)	69 (56.1)
Safety Population	40 (100.0)	83 (100.0)	123 (100.0)
6-11 years	18 (45.0)	36 (43.4)	54 (43.9)
12-16 years	22 (55.0)	47 (56.6)	69 (56.1)
Modified Cognitive ITT Population	40 (100.0)	81 (97.6)	121 (98.4)
6-11 years	18 (45.0)	34 (41.0)	52 (42.3)
12-16 years	22 (55.0)	47 (56.6)	69 (56.1)
Modified Efficacy ITT Population	40 (100.0)	83 (100.0)	123 (100.0)
6-11 years	18 (45.0)	36 (43.4)	54 (43.9)
12-16 years	22 (55.0)	47 (56.6)	69 (56.1)
Cognitive PP Population	36 (90.0)	66 (79.5)	102 (82.9)
6-11 years	16 (40.0)	24 (28.9)	40 (32.5)
12-16 years	20 (50.0)	42 (50.6)	62 (50.4)
Efficacy PP Population	37 (92.5)	67 (80.7)	104 (84.6)
6-11 years	16 (40.0)	25 (30.1)	41 (33.3)
12-16 years	21 (52.5)	42 (50.6)	63 (51.2)

Abbreviations: ESL = eslicarbazepine acetate; ITT = intent-to-treat; PP = per-protocol.
Note: Percentages are calculated based on the total number of randomized patients.

Outcomes and estimation

- Neurocognitive results

For the primary endpoint of Power of Attention, at the end of double-blind period, the 95% CI for the difference of LS means between placebo and ESL was (-137.593 ms, 203.993 ms) for the overall age group, (-356.364 ms, 407.110 ms) for the age group of 6 to 11 years and (-146.578 ms, 186.835 ms) for the age group of 12 to 16 years. The lower bounds of these CIs were smaller than -121 ms, and thus non-inferiority could not be shown. The difference between the two conditions at the end of the double-blind period was 57 msec in favor of ESL; the Glass' Effect size of this superiority being 0.28.

In superiority tests for the Power of Attention, there was no significant difference between ESL and placebo for the overall age group or among the 2 age groups (all $p>0.48$).

Of the four secondary cognitive domains assessed in this study, ESL was found not to negatively influence sustained attention, working memory, or memory retrieval speed. ESL did have a statistically reliable negative effect on the Episodic Memory Index, a measure of delayed recognition of previously presented information.

However, the two groups had notably different pre-study scores on this measure, the ESL group being initially superior to placebo, and the effect may instead have represented 'regression to the mean'.

- Other study outcomes

Standardized seizure frequency was generally lower in the ESL treatment group compared with placebo. The least square mean of the relative reduction in standardized seizure frequency during the maintenance period was 34.82 % (SE: 10.27, 95% CI: -55.16, -14.49) for the ESL group versus 13.84 % (SE: 13.77, 95% CI: -41.12, 13.44) for the placebo group. The non-parametric analysis, showed a statistically significantly difference in favour of ESL compared with placebo in both the Modified Efficacy ITT and Efficacy PP populations ($p<0.001$).

There was no rebound effect observed in the subset of patients who completed the tapering-off period.

The results from the analyses of the other efficacy endpoints in the Modified Efficacy ITT population, including the proportion of responders during the maintenance period, were consistent with the results for the standardized seizure frequency. The proportion of patients who had at least a 50% reduction from baseline in standardized seizure frequency during the mantenance period was higher in the ESL group (50.6%) compared to placebo (25.0%) and the difference compared with placebo was statistically significant ($p=0.009$). During the titration + maintenance period, the percentage of responders was 27.5% in the placebo group and 48.2% in the ESL group ($p=0.038$).

There were no statistically significant treatment-by-age group, treatment-by-sex, or treatment by country interactions in the analysis of standardized seizure frequency during the maintenance period, thus indicating that the treatment effect was consistent in each age group, sex, and country.

There were no differences between the two groups in Global cognitive skills, social competence and QOL at the end of double blind period.

2.5.2.3. Summary of main study(ies)

The following tables summarise the efficacy results from the main studies 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 13 – Summary of Efficacy for trial 305

Title: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial.		
Study identifier	BIA-2093-305 (part I)	
Design	The study consisted of 5 parts as follows: Part I: parallel-group, randomised, placebo-controlled study. Part II: Optional 1-year open-label extension for subjects completing Part I. Part III to V: Optional open-label extension periods (Parts III and IV = 1-year, Part V = 2-years) for subjects who had completed the previous part.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks (maintenance period) 8 weeks (observational baseline period) 6 weeks (titration period) 4 weeks observation follow-up 4 subsequent optional open-label extension phases (parts II-V)
Hypothesis	Superiority	

Treatments groups	ESL		ESL 10-30 mg/kg/day QD (maximum 1200 mg/day) as oral suspension (2-6 years of age) or tablets (7-18 years), 155 patients randomised
	Placebo		QD placebo oral suspension or tablets, 149 patients randomised
Endpoints and definitions	Co-Primary endpoint (I)	50% responder rate	Responder rate, defined as the proportion of patients with at least a 50% decrease in the standardized 4-week seizure frequency from the baseline period to the 12-week maintenance period
	Co-Primary endpoint (II)	% reduction POS frequency	Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period
Database lock	Last patient completing part I: 20 August 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 12 weeks maintenance treatment		
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**ESL**
	Number of subject	**129**	**134**
	50% responder rate, n (%)	40 (31.0)	41 (30.6)
	% reduction in seizure frequency, LS mean	-8.6	-18.1
	Standard Error (95% CI)	5.93 (-20.24, 3.12)	5.84 (-29.58, -6.60)
Effect estimate per comparison	Co-Primary endpoint I: 50% responder rate	Comparison groups	Placebo vs ESL
		Odds ratio	0.97
		95% CI	0.57; 1.63
		P-value	0.2001
	Co-Primary endpoint II:% reduction in seizure frequency	Comparison groups	Placebo vs ESL
		LS mean difference	9.5
		95% CI	-6.71; 25.77
		P-value	0.2490
Notes	N/A		

Analysis description	**Subgroup analysis by age strata**		
Analysis population and time point description	Intent to treat Stratum I: age 2-6 years, stratum II: age 7-11 years and stratum III: 12-18 years		
Descriptive statistics and estimate variability	**Treatment group**	**Placebo stratum II+III**	**ESL stratum II+III**
	Number of subject	**96**	**103**
	50% responder rate, n (%)	29 (30.2%)	36 (35.0)

	% reduction in seizure frequency, LS mean	-10.5	-24.4
	Standard Error (95% CI)	6.12 (-22.58, 1.56)	5.91 (-36.09, -12.79)
Effect estimate per comparison	Co-Primary endpoint I: 50% responder rate	Comparison groups	Placebo vs ESL
		Odds ratio	1.24
		95% CI	0.68; 2.25
		P-value	0.4759
	Co-Primary endpoint II:% reduction in seizure frequency	Comparison groups	Placebo vs ESL
		LS mean difference	13.9
		95% CI	-2.89, 30.74
		P-value	0.1040
Notes	*A statistically significant difference in favour of ESL over placebo was observed in an analysis of the relative change in standardised seizure frequency during the titration+maintenance period based on patients in strata II and III (difference 16.2%; 95% CI: -1.08, 31.32, p=0.0359).*		

Table 14 - Summary of Efficacy for trial 208

Title: Effects of eslicarbazepine acetate (BIA 2-093) on cognitive function in children with partial onset seizures: an add-on, double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial			
Study identifier	BIA-2093-208 (part I)		
Design	The study consisted of three parts: Part I: multicenter, double-blind, randomized, placebo-controlled, parallel-group clinical study Part II: one-year, open-label, uncontrolled extension Part III: two-year open-label extension.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks (4-week up-titration and 8-week maintenance) 4 weeks (observational baseline period) 4 weeks (observational follow-up) 2 subsequent optional open-label extension phases (parts II and III)
Hypothesis	Superiority		
Treatments groups	ESL		ESL 10-30 mg/kg/day QD (maximum 1200 mg/day) as tablets, 83 patinets randomised
	Placebo		QD placebo as tablets, 40 patients randomised
Endpoints and definitions	Secondary endpoint	% reduction seizure frequency	Relative reduction from baseline in standardised (4-week) seizure frequency over the evaluation period
	Secondary endpoint	50% responder rate	Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period to the 8-week maintenance period
Database lock	Last patient last visit (Part I): 21 March 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Modified Efficacy ITT population: all randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment Time point: see above		
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**ESL**
	Number of subject	**40**	**83**
	% reduction in seizure frequency, LS mean	-13.84	-34.82
	Standard Error (95% CI)	13.77 (-41.12, 13.44)	10.27 (-55.16, -14.49)
	50% responder rate, n (%)	10 (25.0%)	42 (50.6%)
Effect estimate per comparison	Secondary endpoint: % reduction in seizure frequency	Comparison groups	Placebo vs ESL
		LS mean difference	-20.99
		P-value (non-parametric analysis)	<0.001
	Secondary endpoint I: 50% responder rate	Comparison groups	Placebo vs ESL
		P-value	0.009
Notes	*The main objective of the study was to explore any possible negative effect of ESL on cognitive function in children (primary endpoint: Power of Attention)* *Efficacy analyses were also conducted on the Efficacy PP populations and the results were in line with the Modified Efficacy ITT population.*		

Analysis performed across trials (pooled analyses and meta-analysis)

- **Meta-analysis of key phase 2 and 3 studies 208 and 305**

The key Phase 2 and 3 studies (Study 208 and Study 305) shared many design features, objectives, inclusion and exclusion criteria, endpoints and statistical analytical approach. The MAH conducted a meta-analysis of data from both Study 208 and Study 305 for children from Europe aged 6 to 16, i.e. across age subgroups 6 to 11 and 12 to 16 years in order to evaluate whether the combination of results supports additional evidence of efficacy of ESL. Table 19 summarised the selected analysis population.

Table 15 – Overview of Meta-Analysis Set

Criterion	208	305	Meta Analysis
Age (years)	6-16	2-18	6-16
Age stratum	6-11 / 12-16	2-6 years / 7-11 years / 12-18 years	6-11 / 12-16
Regions	Europe N=123	Europe N=284 Asia N=20	Europe N=407
Dose (during maintenance)	30 mg/kg/day (maximum 1200 mg/day)	20-30 mg/kg/day (maximum 1200 mg/day)	20-30 mg/kg/day (maximum 1200 mg/day)
Analysis set	ITT	ITT	ITT

Note: N denotes the number of randomised patients.

Analysis variables were:

1. Relative reduction of standardised seizure frequency during maintenance therapy.

2. Absolute reduction of standardised seizure frequency during maintenance therapy.

Only one of the two primary efficacy endpoints (relative change in standardised seizure frequency) of study 305 was chosen as endpoint in the meta-analysis. Response to treatment, which is the recommended primary endpoint for POS add-on trials according to the CHMP Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (hereafter referred to as Epilepsy Guideline), was not included in the meta-analysis.

The meta-analysis across age subgroups assumed that the age subgroups were independent and that the variation between age subgroup applied just as much within studies as across studies. Using the harmonised meta-analysis set, the single studies were reanalysed using ANCOVA that modelled the reduction in seizure frequency (absolute and relative) as a function of age using 3 different models (age stratified, age continuous, and no age as co-factor), using the least square means of the difference of ESL to placebo, and the mean square error. The between study variance in the random effects approach was estimated according to the methods of moments (DerSimonian and Laird).

Results

The meta-analysis set comprises 323 patients. Since 18 of the 20 patients from Asia are younger than 6 years, only 2 additional patients were excluded because of their Asian origin.

The results for the individual studies as well as the combined estimate indicate that the reduction in absolute seizure frequency is higher after treatment with ESL compared to placebo. Consistent estimates for the combined study effects were observed across the 3 applied models. Confidence intervals for the studies combined are all greater than zero indicating that the treatment with ESL reduces the absolute seizure frequency for children aged 6 to 16 years in Europe (p-values < 0.01).

As for the results for the relative change from baseline, a reduction of seizure frequency of about 14-15% was estimated for ESL versus placebo in the 3 models; the relative contribution was higher from the 208 study (22%) versus the 305 study (13%). When age was used as a covariate in the models, either as a stratified or a continuous covariate, the variability increases, suggesting that age has an impact on the efficacy variables.

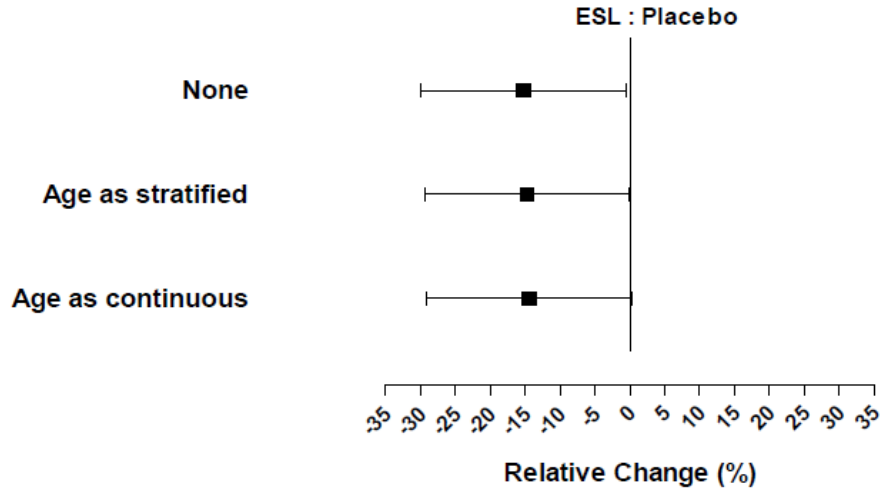


Figure 5 – Relative difference in standardised seizure frequency adjusted for baseline seizure frequency

2.5.3. Supportive study data

- **Study BIA-2093-202**

Study 202 was an open-label, single-centre, multiple-dose study. It was planned to recruit 30 paediatric epileptic subjects with 10 subjects in each of the following age groups: 2 to 6 years [Group 1], 7 to 11 years [Group 2], and 12 to 17 years [Group 3]. The study had previously been submitted an was reviewed in the context of the initial marketing authorisation application of Zebinix in the EU. Relevant PK results are summarised in section 2.4. of this report.

The primary study objective was to characterise the PK of ESL in children and adolescents with epilepsy. Secondary objectives included the assessment of efficacy and tolerability. The secondary efficacy variables were percentage change in seizure frequency during each 4-week treatment period compared to the baseline phase and percentage of patients who became seizure-free. All secondary variables were analysed exploratory.

The study comprised a 4-week baseline phase, followed by 3 consecutive 4-week treatment periods with ESL in which subjects received ESL QD at the following dosage regimens: 5 mg/kg/day (weeks 1–4), 15 mg/kg/day (weeks 5–8) and 30 mg/kg/day or 1800 mg/day, whichever was less (weeks 9–12). After the last treatment period or in the event of premature discontinuation, the dose was down-titrated over a 2-week period.

For Group 1 (2–6 years), patients received ESL oral suspension 50 mg/mL. The dose was to be rounded to the nearest 25 mg unit. For Group 2 (7–11 years) and Group 3 (12–17 years), ESL strengths 200 mg, 400 mg, 600 mg and 800 mg tablets could be used. The dose was to be rounded to the nearest 100 mg unit. Half tablets might be used for dosage adjustment (tablets were scored).

Efficacy results

A dose-dependent decrease in relative (%) seizure frequency was observed in Group 1 (2-6 yrs) and Group 3 (12-17 yrs). In Group 1, the median relative (%) change in seizure frequency in relation to baseline was -28.2% (95%CI: -60, 13) during the 5 mg/kg/day treatment period, - 24.8% (95%CI: -93, -6) during the 15 mg/kg/day treatment period, and -40.6% (95%CI: -86, -4) during the 30 mg/kg/day treatment period. In Group 3, the median relative (%) change in seizure frequency in relation to baseline was -17.1% (95%CI: -56, 30) during the 5 mg/kg/day treatment period, -31.7% (95%CI: -71, 19) during the 15 mg/kg/day treatment period, and -43.1% (95%CI: -77, 21) during the 30 mg/kg/day treatment period. No noticeable dose-dependent change was observed in seizure frequency in Group 2 (7-11 yrs), for any of the dose levels.

One patient in each age group became seizure-free.

- **Long-term efficacy data**

Study 305 (Part II-V)

In Study 305, 4 long-term open-label extension periods followed the completion of the double-blind part I of the study. Data from these extension periods had previously been submitted and were reviewed by the CHMP. A summary is presented below.

Within Part I of the study, patients had to complete a tapering-off period after the double-blind maintenance period. For patients who continued in the 48-week Part II, the ESL starting dose was 10 mg/kg/day (maximum 800 mg/day). The dose was titrated according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to a maximum of 1200 mg/day). Down-titration was allowed. After completion of Part II, patients had the option to further continue treatment in in up to 3 subsequent open-label extension periods: Part III (1 year), Part IV (1 year), and Part V (2 years).

The study designs of the 1-year extension Parts III and IV were identical and consisted of a 48-week open-label extension period. Part V was a 2-year open-label extension period and the last planned period of the study. In each of Parts III, IV, and V, the starting ESL dose was the same dose that the patient was receiving at the end of the previous extension period (i.e. Parts II, III, and IV, respectively), unless the investigator decided to titrate this dose to achieve further reduction in seizure frequency or due to the occurrence of any intolerable adverse events (AEs). The daily dose could be titrated in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight).

If the patient did not continue receiving ESL after an open-label extension period or in case of early discontinuation of ESL during an open-label extension period, the respective patient entered a tapering-off/follow-up period, in which study treatment was down-titrated and standard antiepileptic treatment introduced.

Results

Of the 267 subjects who completed Part I of the study, 260 subjects were enrolled into Part II and 183 patients completed Part II. Subsequently, 152 subjects were enrolled into Part III. Of these, 65 subjects had received ESL and 87 subjects had received placebo during the double-blind part (Part I) of the study. Four subjects (2.6%) completed open-label treatment with ESL through Part V. The number of patients was:

- Treated in Part I: 304 patients (155 with ESL, 149 with placebo).
- Treated in Part II: 260 patients (128 with ESL in Part I, 132 with placebo in Part I).
- Treated in Part III: 152 patients (65 with ESL in Part I, 87 with placebo in Part I).

- Treated in Part IV: 81 patients (37 with ESL in Part I, 44 with placebo in Part I).
- Treated in Part V: 56 patients (27 with ESL in Part I, 29 with placebo in Part I).
- Analysed for efficacy in Part II: 225 patients (ITT)
- Analysed for efficacy in Part III-V: 148 patients (ITT).

The most common reasons for discontinuation in Part II were lack of efficacy (24 patients [9.2%]) and patient's (or legally authorised representative's) wish (23 [8.8%]). These reasons were more frequently reported in the previous (Part I) ESL group than in the previous placebo group. The most frequent reason for study discontinuation during parts III-V was due to switch to continued treatment with ESL as part of a compassionate use program. During study parts III, IV or V, respectively 0%-5.3% of study subjects discontinued due to lack of efficacy and 0% -0.7% discontinued due to "adverse event".

Two baseline periods were defined as reference periods in efficacy analyses of Parts III-V: Baseline Part I and Baseline Part III–V. The latter referred to the last 4 weeks (in Part II) prior to first intake (Day 1) in Part III–V.

- The total responder rate during Part II was 46.7%. Responder rates steadily increased during Part II, from 44.9% during weeks 1-4 to 57.5% during weeks >40.

  The total responder rate during Part III–V was 25.7% when compared to Baseline Part III-V. Total responder rates steadily increased up to 50.0% during weeks 181-192, and then decreased to 25.0% during weeks >192.

- The total median standardised seizure frequency during Part II was 6.1, resulting in a median relative change compared to the baseline period of -46.7%. The median relative change was larger in the previous placebo group (-51.4%) than in the previous ESL group (-40.4%). The total median standardised seizure frequency decreased from 7.0 during weeks 1-4 to 4.0 during weeks >40.

  The total median standardised seizure frequency during Part III-V was 2.6, resulting in a median relative change from baseline part III-V of -21.4% (and from baseline part I of -75.5%). The median relative change from baseline part III-V increased up to weeks 181-192 (to -40.5%).

<u>Study 208 (Part II-III)</u>

Study 305 included 2 open-label extension periods (Part II: 1 year and III: 2 years). Data from these extension periods had previously been submitted and were reviewed by the CHMP. A summary is presented below.

Part II started after completion of the last 2-week, 10 mg/kg/day down-titration step in Part I. All patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). At the end of Part II, patients either entered a tapering-off/follow-up period or an additional two-year open-lavbel extension (Part III). Patients could begin Part III on the same dose that they were taking at the end of Part II. The dose range was 10 to 30 mg/kg/day (maximum allowed ESL dose of 1200 mg QD), and was titrated up or down by the investigator according to clinical response or in case of intolerable adverse events (AEs). Upon completion of this extension, patients were tapered off ESL in 10 mg/kg/day steps every 2 weeks.

Results

A total of 112 patients (100.0%) completed the double-blind maintenance period (Part I) and entered Part II. All 112 patinets were included in the Safety and the Modified Efficacy ITT Population. Of the 95 patients who completed Part II, a total of 42 patients entered Part III. All 42 patients were included in the Safety Population,

and 41 patients were included in Modified Efficacy ITT Population. The primary reason for premature discontinuation from study Part II and III was request of patient/caregiver/parent.

In Part II, the median relative change in seizure frequency from baseline during the one-year open-label period was -64.76 overall, and -59.57% in the previous (double-blind, part I) placebo group and -65.47% in the previous ESL group. The percentage of 50% responders was 61.6 % overall, and 54.1% in the former placebo and 65.3% in the former ESL groups. The percentage of responders increased over time in both treatment groups. The percentage of responders for children aged 6 to 11 years was 63.0% and 60.6% for adolescents aged 12 to 16 years. Further, in Part II, patients showed a mean improvement in Power of Attention of 182 ms (235 ms for the 6 to 11 year old patients and 144 for the 12 to 16 year old patients).

In part III, efficacy endpoints included treatment retention time (defined as actual time on treatment) and clinical global expression severity scale change from baseline. Using Kaplan-Meier methods, the median treatment retention time was sestimated to be similar in the previous ESL treatment group (734 days) and the previous placebo group (739 days). The results of this analysis in each of the two age groups were similar to the overall results. Overall, 31 (75.6%) patients remained on treatment during Part III. With regards to the clinical global expression severity scale, overall, at the last assessment, there was a slight mean reduction from baseline in the severity of illness (-0.5); all other categories were unchanged from baseline. Results were similar for the previous placebo and ESL groups as well as for the two age groups (6 to 11 years and 12 to 16 years).

2.5.4. Discussion on clinical efficacy

All clinical trials submitted in support of this application have previously been reviewed by the CHMP, however not with a view to supporting an extension of the indication of Zebinix to the paediatric population. The discussion in this chapter therefore focuses on relevant aspects for establishing efficacy of Zebinix in the proposed extended target population of children aged 2 years and above, and as later corrected to 7 years and above.

Data from 3 clinical trials were submitted to support efficacy of ESL in the add-on treatment of POS in children. The main support was derived from two pivotal studies, the phase 3 trail 3 BIA-2093-05 and the phase 2 study BIA-2093-208. Both studies were double-blind and placebo controlled with a minimum duration of the maintenance period of 8 weeks (study 208) and 12 weeks (study 305), respectively. ESL was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. Whereas in study 208 the targeted dose was 30 mg/kg/day, the initial target dose in study 305 was 20 mg/kg/day, which could be further titrated to 30 mg/kg/day only during the titration period.

In addition, the CHMP noted that partial epilepsies in children older than 4 years have a similar clinical expression as partial epilepsies in adolescents and adults. Therefore, in line with the CHMP Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (hereafter referred to as Epilepsy Guideline), the results of efficacy trials performed in adults with refractory partial epilepsies, could to some extent be extrapolated to children provided the dose is established. For Zebinix, efficacy for the add-on treatment of adults with POS with or without secondary generalisation has been established at the time of the initial marketing authorisation, based on the results of 3 pivotal studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303).

With regards to the data submitted with the present application, the phase 3 efficacy study 305 was originally planned as a stand-alone trial to investigate ESL as adjunctive treatment in children with refractory POS aged 2 to 18 years, but it failed to demonstrate superiority of ESL compared to placebo. For both primary efficacy variables, 50% response rate (percentage of patients with a reduction in POS seizures by at least 50%) and

relative change in standardised (4-week) POS frequency, no statistically significant difference between ESL and placebo was found. Of the 134 patients in the ITT set who received ESL, 41 patients (30.6%) were responders compared to 40 out of 129 patients (31.0%) in the placebo group, resulting in a non-significant odds ratio of 0.97 (95% confidence interval [CI]: 0.57, 1.63; p=0.9017). LS mean relative change in standardised seizure frequency was higher in the ESL group (-18.1%) than in the placebo group (-8.6%), resulting in a statistically non-significant difference of 9.5% (95% CI: -6.71, 25.77; p=0.2490). There was also a trend in favour of ESL compared to placebo when the standardised seizure frequency was calculated based on the titration + maintenance period (instead of the maintenance period as per the primary efficacy analysis) and also when the ITT set is restricted to patients from age strata II (7-11 years) and III (12-18 years). However, between-treatment differences were still not statistically significant. The only statistically significant difference in favour of ESL over placebo was observed in a post-hoc analysis combining the above-mentioned restrictions, i.e. analysing the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III (difference 16.2%; 95% CI: -1.08, 31.32, p=0.0359). Notably, the observed therapeutic effect in the placebo group was larger than anticipated, while that in the ESL group was lower than expected when the study was planned.

Study 208 was primarily designed as a non-inferiority study in children aged 6 to 16 years with safety variables as primary endpoint (which was not met) and efficacy outcomes as secondary endpoints. The efficacy analysis of study 208 showed a statistically significant difference in favour of ESL compared to placebo in both relative reduction in standardised seizure frequency (LS mean difference of -20.99, p<0.001) and the proportion of patients with a 50% or greater reduction in seizure frequency (50.6% for ESL vs. 25.0% for placebo, p=0.009). Subgroup analyses for responder rate and relative change in standardised seizure frequency were consistent with the overall study results for both age groups (6-11 and 12-16 years). However, the efficacy results of this study should be interpreted with caution because the study was not designed for accurate assessment of efficacy.

Finally, study 202 was an uncontrolled, open-label PK study and efficacy data from this study were considered only supportive. The study recruited 10 patients each in 1 of 3 age groups and showed a dose-dependent decrease in relative (%) seizure frequency in age group 1 (2-6 years) and group 3 (12-17 years), but not in group 2 (7-11 years).

Finally, the MAH presented long-term efficacy data from open-label follow-up studies of study 305 and 208. The data suggested that efficacy was either maintained or improved over time. Although this is reassuring, the CHMP was of the view that, due to the open-label design and the high drop-out rates, no robust conclusions could be drawn from these data.

Preliminary study findings of 208 and 305 had previously been presented for the purpose of receiving EMA scientific advice. At that time, the CHMP considered the data package unlikely to be adequate for an extension of the ESL marketing authorisation for use in paediatric patients. Specifically, the CHMP noted that additional information was required in order to provide a better understanding of the results observed in study 305, including potential PK issues in children. In order to address these concerns, the MAH conducted additional analyses including population PK and exposure-efficacy analyses based on a population PK model that is specific to paediatrics (see section 2.4) and a meta-analysis of efficacy data from study 208 and study 305 in the 6-16 year old age range that was common across the studies.

With regards to the meta-analysis, the CHMP was of the view that the approach to combine studies 208 and 305 in a meta-analysis, which was not pre-specified but rather performed post-hoc after the study results were available, was problematic. As stated in the EMA 'Points to Consider on Applications with meta-analyses and one pivotal study' (CPMP/EWP/2330/99), "*a meta-analysis of two studies originally intended to stand on their own is*

not expected to add any useful information. In particular, a meta-analysis cannot be used to reconcile the conflicting results of one positive and one inconclusive study." Data-driven decisions with regard to the design of the meta-analysis could not be excluded. In this context, the CHMP noted that the study population of the meta-analysis did not correspond to the claimed extended target population which initially also included children aged 2-5 years. Considering that a lower proportion of responders were observed in the subgroup of 2-6 year old patients in study 305 receiving ESL compared to placebo, the decision to exclude younger children from the pooled analysis is striking. Furthermore, only one of the two primary efficacy endpoints (relative change in standardised seizure frequency) of study 305 was chosen as endpoint in the meta-analysis. Response to treatment, which is the recommended primary endpoint for POS add-on trials according to the CHMP Epilepsy Guideline, was not included; for this endpoint, no difference (not even a numerical one) between treatments had been observed in study 305. Further uncertainty arose from the use of the random effects model according to DerSimonian and Laird, for which inflation of the type I error has been reported for meta-analyses including a small number of studies. Beside these methodological caveats, the results of the meta-analysis were not convincing. For the endpoint of relative change in standardised seizure frequency, the p-value for the three ANCOVA models used (age according to 2 strata, age as continuous covariate, and no age as co-factor), ranged between 0.042 and 0.055 and lower bounds of the pooled 95% CIs were close to 0 (range -0.29 to 0.52). Usually, p-values substantially smaller than 0.05 and lower bounds of pooled 95% CIs well away from 0 are expected for a meta-analysis aiming to establish a convincing effect (CPMP/EWP/2330/99). Overall, the CHMP considered that the meta-analysis did not allow robust conclusions on the efficacy of ESL.

Further efforts in the evaluation of this application focussed on the reasons for the inconsistent outcome of studies 305 and 208 and in particular possible reasons that could explain the failure of study 305. The MAH considered the inclusion of the 2-6 years age group and under-dosing in this age group as a key factor for the failure of study 305. In addition to a reduced exposure in the youngest age group (see section 2.4. for details), the MAH also noted that although the underlying disease is the same for children, difficulties in recognising or identifying simple partial seizures in very young children, particularly for the 2-6 years group, could have been a contributing factor to the study outcome as well as the high pacebo response rate. Considering the poor efficacy observed in children 2-6 years and the difference in PK compared to older children, the MAH proposed to narrow the proposed indication to children > 6 years, which was agreed by the CHMP.

In an attempt to further explore possible differences bewteen studies 305 and 208, and in response to a request by the CHMP, the MAH presented analyses of the demographics and baseline characteristics of the recruited children above 6 years of age. The analyses were restricted to stratum 2+3 of study 305 (children > 6 years) as by this time the MAH had proposed to exclude younger children from the extended target population. Heterogeneities were observed for gender, age group, weight, BMI, age at onset of epilepsy, duration of epilepsy, seizure frequency at baseline and worst seizure type. According to the MAH, the results indicated a pronounced signal for an influence of seizure frequency at baseline and age at onset or duration of epilepsy. In view of the MAH, in particular, the differences in age at onset and duration of epilepsy might explain the smaller treatment effect of ESL in study 305 when compared to study 208. However, the CHMP did not agree with this conclusion as relative reduction in standardised seizure frequency was not relevantly influenced by baseline seizure frequency, and effect of age at onset and duration of epilepsy was not consistent in studies 208 and 305 such that these factors cannot convincingly explain different outcomes in studies 208 and 305. It was not expected that additional analyses would provide further clarification. As previously discussed, inclusion of the 2-6 years age group and under-dosing in this age group were considered the most likely explanation for the failure of study 305.

There were furthermore doubts if a maintenance dose of 20 mg/kg/day, as proposed by the MAH for use in clinical practice, was sufficient to achieve adequate exposure and efficacy in children > 6 years. Even if only

children above 6 years from study 305 (stratum 2+3) are considered, the observed treatment effects were substantially lower than in study 208; the LS mean difference between ESL and placebo of the change in standardised seizure frequency during the mainatenance period was 13.9% for stratum 2+3 in study 305 (p=0.1040) and -20.99 (p<0.001) in study 208. This raises the question if the difference in the efficacy outcomes of study 305 and 208 could be due to differences in the administered doses: While the target dose in study 208 was 30 mg/kg/day (83% of ESL patients were titrated to this dose), the target dose in study 305 was 20 mg/kg/day and only 39% of patients were titrated to the maximum allowed dose of 30 mg/kg/day or or 1200 mg/day, whichever was less. Additional analyses by the MAH showed that the 50% response rates and change in relative reduction of standardized seizure frequency were larger in children receiving the 30 mg/kg/day dose compared to 20 mg/kg/day or all doses combined. However, analyses for the 20 mg/kg/day dose showed a larger placebo effect, which is likely due to the fact that patients in the placebo arm at the 20 mg/kg/day dose level who were not 'up-titrated' were likely those less susceptible to seizures compared to those who were up-titrated. The observed larger effect size in the placebo arm for the 20 mg/kg/day dose level was thus not surprising and may explain to some extent the smaller effect size for ESL at this dose level. In general, subgroup analyses according to dose are generally difficult to interpret in a study involving titration according to efficacy as comparisons are not based on randomised groups and thus, no firm conclusions could be drawn from these data.

While efficacy of the 20 mg/kg/day dose has not been convincingly established, the CHMP considered that population PK simulations have shown comparable exposure to eslicarbazepine at a dose of 20 mg/kg/day in children > 6 years and at 800 mg/day in adults. The same applies to the paediatric dose of 30 mg/kg/day and the adult dose of 1200 mg/day. Both 800 mg/day and 1200 mg/day doses have previously been shown to be effective doses in adults and are currently approved for use in add-on therapy of POS. Based on the comparative exposure findings and given that disease expression of partial epilepsies is similar in adults, adolescents and children, the CHMP was of the view, that an extrapolation of the established efficacy of ESL in adults to children down to 7 years of age was possible at the proposed maintenance dose range.

Dose recommendations including an increase of the dose up to 30 mg/kg/day (with a maximum daily dose of 1200 mg) based on individual response were agreed. The CHMP also agreed to recommend a starting dose of 10 mg/kg/day and dose titration by increases of 10 mg/kg/day increments after one or two weeks based on individual response. This approach is equivalent to the dosing recommendations for adults.

2.5.5. Conclusions on the clinical efficacy

Although the reason for the failure of study 305 cannot be finally explained, the CHMP was of the view that factors such as underestimation of the efficacious dose range in particular in the youngest age group of 2 to 6 year old children and a high response to placebo are likely to have played a role. Population PK simulations suggest that exposure to eslicarbazepine at doses of 20 mg/kg/day and 30 mg/kg/day in children > 6 years is comparable to the adults at doses of 800 mg/day and 1200 mg/day, both of which have previously been shown to be effective in the adjunctive therapy of adults with POS.

Based on the above and since disease expression of partial epilepsies is similar in adults, adolescents and children, the CHMP concluded that the application for an extension of the indication to adjunctive therapy in adults, adolescents and children aged above 6 years, with POS with or without secondary generalisation was acceptable from an efficacy point of view.

2.6. Clinical safety

For the safety analysis, clinical safety data were organsied in 2 groups: **Paediatric studies** and **adult studies** (integrated analysis of Part I of studies 301, 302, 303 and 304 together with study 201).

The primary basis for the paediatric safety assessment was an integrated analysis of study 305 and 208 result.

In addition, amongst the paeditaric studies, dat were presented as follows:

- individual data from Part I (double-blind part) and II (open-label extension periods) of study 305 and 208, respectively,
- long-term data from 305 and 208 open-label extensions III to V and III, respectively, and
- supportive data from 202 (not placebo-controlled)

The focus of the safety analysis is on treatment-emergent adverse events (TEAEs). In the integrated key Phase 2/3 paediatric studies, TEAEs during Part I were defined as adverse events (AEs) that developed or worsened during the on-treatment period (defined as the time from first dose until 28 days after the last dose or date of the follow-up Visit 1 for subjects continuing in Part II of the respective studies). All AEs with an onset date or that worsened after the first dose in Part II until the end of the 1-year open-label period were reported in the analysis of Part II. Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 was used for coding of reported AE terms.

In addition to descriptive summaries of all TEAEs, serious TEAEs, TEAEs by relationship, by intensity and leading to discontinuation of study medication were evaluated.

In all the paediatric studies, assessment of the relationship/causality of a TEAE to the administration of the study medication was a clinical decision by the investigator based on all available information at the time of the completion of the case report form.

Patient exposure

In the completed clinical studies at the cut-off of date of 21 April 2015, ESL at any dose was administered to a total of 438 children aged 2-18 years with POS in 2 Phase 2 studies (202 and 208, contributing 151 ESL treated patients) and 1 Phase 3 study (305, contributing 287 ESL-treated patients). Analysis populations including the safety set for studies 305 and 208 are shown in Table 4 and Table 9.

During the placebo-controlled Part I of the integrated key Phase 2/3 paediatric studies, a total of 238 children received ESL (48 subjects were 2 to 5 years old, 95 subjects were 6 to 11 years old and 95 subjects were 12 to 18 years old). A total of 234 subjects (98.3%) had a cumulative exposure (includes the titration, maintenance and tapering-off periods) of up to 6 months with a total treatment period of 80.5 person years. Mean treatment duration with ESL in Part I was 81.1 days in study 208 and 140.9 days in study 305.

A total of 372 children received ESL in Part II, the 1-year extensions, of the integrated key Phase 2/3 paediatric studies (77 subjects were 2 to 5 years old, 147 subjects were 6 to 11 years old and 148 subjects were 12 to 18 years old). The majority (99.7%) had a cumulative exposure of up to 18 months with a total treatment period of 311.1 person years. The mean treatment duration with ESL during Part II was 331.7 days in study 208 and 298.7 days in study 305.

The longest exposure to ESL as adjunctive therapy in epileptic children was up to 65 months (5.5 years) in subjects who continued therapy with ESL in open-label extensions of Study 305.

Table 13 provides a summary of exposure by dose for Phase I of studies 208 and 305. The majority of subjects received a dose of up to 30 mg/kg/day QD (83.1%) at the start of the maintenance period.

Table 16 – Estimated ESL dose at the start of the maintenance period of Part I in the Phase 2/3 paediatric studies - Study 208 and Study 305 (safety population)

Dose at start of double-blind maintenance period	Number (%) of subjects			
	Study 208		Study 305	
	Placebo	Total ESL	Placebo	Total ESL
Entered maintenance period	40	76	124	128
1200 mg	0	0	2 (1.6)	3 (2.3)
30 mg/kg/day	37 (92.5)	69 (83.1)	62 (50.0)	59 (46.1)
20 mg/kg/day	3 (7.5)	3 (3.6)	57 (46.0)	60 (46.9)
10 mg/kg/day	0	4 (4.8)	3 (2.4)	5 (3.9)
Prescribed dose not per protocol	-	-	0	1 (0.8)[a]

ESL = eslicarbazepine acetate.
[a.] Subject 13108 received 24 mg/kg/day (daily dose: 800 mg/day).

Adverse events

- **Overview of the main results for study 208 and 305**

Study 305, Part I

Overall TEAE incidence was 83.6% in the ESL group compared to 72.9% in the placebo group. Most frequently reported TEAEs (>5% of patients in any treatment group) were headache (13.4% ESL, 6.2% placebo), nasopharyngitis (11.2% ESL, 11.6% placebo), somnolence (11.2% ESL, 4.7% placebo), convulsion (9.7% ESL, 10.9% placebo), pyrexia (7.5% ESL, 5.4% placebo), pharyngitis (6.7% ESL, 7.0% placebo), vomiting (6.0% ESL, 0.2% placebo), diplopia (6.0% ESL, 1.6% placebo), respiratory tract infection (5.2% ESL, 5.4% placebo), nausea (5.2% ESL, 0.8% placebo), bronchitis (3.7% ESL, 5.4% placebo), and rhinitis (3.0% ESL, 5.4% placebo).

Serious adverse events (SAEs) were reported for 11.2% of subjects on ESL compared to 7.0% of subjects on placebo, including status epilepticus (3 patients [2.2%] ESL, 0 patients placebo), convulsion (2 [1.5%] ESL, 2 [1.6%] placebo), bronchopneumonia (2 [1.5%] ESL, 0 patients placebo), and pneumonia (1 [0.7%] ESL, 3 [2.3%] placebo).

Study 305, part II

Frequencies for AE categories were generally similar between groups by previous treatment with the exception of the period of the first 4 weeks of Part II where more patients previously treated with placebo had TEAEs considered at least possibly related. The reported TEAEs were central nervous system (CNS) related (somnolence, diplopia, and ataxia).

Study 208, part I

The proportion of patients who experienced at least one TEAE was similar between the placebo (47.5%) and ESL (41.0%) groups. TEAEs that were more frequent in the ESL group than the placebo group were respiratory tract infection, including viral, vomiting, diplopia, and allergic dermatitis but these were few overall. Headache was

more frequent in patients receiving placebo compared with those receiving ESL. The incidences for dizziness and somnolence were similar between the placebo and ESL groups.

A total of 5 patients reported at least one treatment-emergent SAE, with 2 patients in the placebo group and 3 patients in the ESL group. One of these patients experienced severe status epilepticus, which was deemed probably related to study drug (ESL). No serious potentially related treatment-emergent events of special interest (cutaneous, cardiovascular, and cerebrovascular) were reported during the study.

Study 208, part II

The proportion of patients who experienced at least one TEAE was slightly higher in patients who received previous double-blind treatment with placebo (45.9%) compared with those who received ESL (37.3%). Headache was more frequent in patients who received previous double-blind placebo (8.1%) compared with those who received previous double-blind ESL (4.0%). Overall, skin and subcutaneous tissue disorders occurred in 4 patients in the previous double-blind placebo group: 1 patient each had dermatitis allergic and ecchymosis, and 2 patients had urticaria.

A total of 8 patients reported at least one treatment-emergent SAE (not considered related to treatment): 4 patients each who received previous double-blind treatment with placebo and ESL.

- **Common adverse events in the integrated phase 2/3 paediatric study safety database**

In the integrated key Phase 2/3 paediatric studies, 66.4% of ESL subjects (158/238 subjects) and 65.1% of placebo subjects (123/189 subjects) reported at least 1 TEAE during Part I (see Table 14).

Table 17 - Summary of TEAEs by age group during Part I of the integrated Phase 2/3 paediatric studies – Study 208 and Study 305 (safety population)

Type of TEAE	Number (%) of subjects							
	2-5 years		6-11 years		12-≤18 years[a]		Total	
	Placebo (N=46)	Total ESL (N=48)	Placebo (N=77)	Total ESL (N=95)	Placebo (N=66)	Total ESL (N=95)	Placebo (N=189)	Total ESL (N=238)
All TEAEs	34 (73.9)	33 (68.8)	50 (64.9)	69 (72.6)	39 (59.1)	56 (58.9)	123 (65.1)	158 (66.4)
At least 1 possibly related TEAE	13 (28.3)	17 (35.4)	8 (10.4)	39 (41.1)	15 (22.7)	29 (30.5)	36 (19.0)	85 (35.7)
Serious TEAEs	6 (13.0)	4 (8.3)	1 (1.3)	7 (7.4)	5 (7.6)	9 (9.5)	12 (6.3)	20 (8.4)
TEAEs leading to discontinuation of investigational product	2 (4.3)	3 (6.3)	1 (1.3)	8 (8.4)	0	2 (2.1)	3 (1.6)	13 (5.5)
TEAEs leading to death	1 (2.2)	0	0	1 (1.1)	0	0	1 (0.5)	1 (0.4)

ESL = eslicarbazepine acetate; N = total number of subjects; TEAE = treatment-emergent adverse event.
[a.] Includes 4 subjects who were 17 years old at admission to Study 305.

The SOCs in which the majority of children reported a TEAE during Part I (>10% of total subjects per treatment group in any SOC) were infections and infestations, nervous system disorders, gastrointestinal disorders and general disorders and administration site conditions. The incidence of subjects with TEAEs in these SOCs was similar for the total ESL and placebo groups.

The most common TEAEs by preferred term were headache (11.8% ESL, 7.9% placebo), somnolence (9.2% ESL, 4.8% placebo), vomiting (7.1% ESL, 4.8% placebo), nasopharyngitis (6.7% ESL, 7.9% placebo) and convulsion (6.7% ESL, 9.5% placebo).

Incidences for ESL subjects between the age groups in the most frequently reported TEAEs were as follows:

- Age group *2 to 5 years*: somnolence (10.4%), pyrexia (10.4%), vomiting (8.3%), viral infection (8.3%) and upper respiratory tract infection (8.3%).
- Age group *6 to 11 years*: headache (11.6%), convulsion (10.5%), diplopia (10.5%) and respiratory tract infection (9.5%).
- Age group *12 to 18 years*: headache (16.8%), somnolence (9.5%), vomiting (7.4%) and nasopharyngitis (7.4%).

The proportion of subjects reporting TEAEs in study Part I was similar across the treatments in each age group (approximately 70% of subjects aged 2 to 5 years, approximately 68% of subjects aged 6 to 11 years and approximately 59% of subjects aged 12 to 18 years). The results were also similar to the proportion of subjects reporting TEAEs in the corresponding age groups during Part II (open-label extension treatment period; 70%, 65% and 60% for age groups 2 to 5 years, 6 to 11 years and 12 to 18 years, respectively).

Possibly related TEAEs were reported by 35.7% of the ESL subjects compared to 19.0% of placebo subjects during Part I, with a similar incidence across the age groups. The SOCs in which the highest percentages of ESL subjects reported possibly related TEAEs (>5% of total ESL subjects) were *nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions and eye disorders*. By preferred term, the most common possibly related TEAEs in the total ESL group were somnolence (8.0% ESL, 4.2% placebo), diplopia (5.0% ESL, 1.1% placebo) and vomiting (4.6% ESL, 1.1% placebo).

In the age group from 2 to 5 years of age, the most common possibly related TEAE observed in more than two patients treated with ESL were somnolence (10.4%); in patients aged from 6 to 11 years treated with ESL the most common possibly related TEAEs were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years these were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%).

In Part II, overall, 23.9% of subjects had TEAEs considered possibly related to ESL (approximately 33%, 25% and 19% for age groups 2 to 5 years, 6 to 11 years and 12 to 18 years, respectively).

Common ADRs (incidence from 1 to ≤10%) in children and adults (incidences from the pooled data from Part I of studies -201, -301, -302, -303, -304), include *diplopia* (incidence in adults 6.9%), *vomiting* (5.5%), *fatigue* (3.3%), *headache* (6.6%), *nausea* (8.0%), *ataxia* (4.1%), and *decreased appetite* (1.2%). Somnolence and dizziness, which have been reported very commonly in adults, are only common in children. Other less common ADRs in children compared to adults include vertigo, asthenia, gait disturbance, tremor, ataxia, balance disorder, vision blurred, diarrhoea and rash. Agitation (1.3%) and abdominal pain (2.1%) were more common in children than in adults.

TEAEs by intensity

The majority of subjects reported intensity of TEAEs to be mild or moderate during Part I (and similarly in Part II). Severe TEAEs were overall similar for total ESL subjects (8.0%; with a similar incidence in Part II) and total placebo subjects (6.9%), but higher in the ESL group than the placebo group for subjects 6 to 11 years. Convulsion was the most common severe TEAE in all the age groups.

TEAEs by dose

See Table 13 for a summary of exposure by dose in the maintenance phases of Phase I of studies 208 and 305.

Upon request by the CHMP, the MAH provided an additional analysis of safety by ESL dose group in all age groups, including all treated patients ≥6 years at baseline in Part I of studies 208 and 305. Patients treated were

grouped according to their planned dose level at the start of the maintenance period. The following treatment groups were established for the purpose of the safety analysis based on the planned dose level at the start of maintenance period: Placebo; ESL dose missing or < 20 mg/kg/day; 20 - < 30 mg/kg/day; 30 mg/kg/day. The analysis of the open-label extensions studied the same subset including only patients who were treated with ESL during the double-blind part and continued in the open-label extension with the same dose level. The overall data set included 190 children exposed to ESL for a period of up to 72 months.

The incidence of all TEAEs and possibly related TEAEs was reduced with increased dose down to frequencies similar for placebo. The same relation was seen in Part II (open-label extensions).

In the group of children ≥ 6 years, 63.0% of placebo subjects and 65.8% of ESL subjects reported at least 1 TEAE during Part I with a decreasing incidence with increasing ESL dose. Possibly related TEAEs were reported by 35.8% of the ESL subjects compared to 17.8% of placebo subjects during Part I, again with a decreasing incidence with increasing ESL dose. TEAEs at least possibly related reported in ESL dosage ≥ 20 mg/kg/day with incidence ≥ 2% were: somnolence (7.6%), diplopia (6.4%), vomiting (3.5%), fatigue (2.9%), dizziness (2.9%), headache (2.9%), and seizure (2.9%).

The overall incidence of serious TEAEs was 10-12% in both double-blind and open-label parts. Serious TEAEs in Part I were found to be higher in ESL subjects compared to placebo in the lower dose groups (<30 mg/kg/day) and similar to placebo for 30 mg/kg/day. In Part II, there was an unexpected high incidence of SAEs in the lowest dose group (<20 mg/kg/d) of 28.9%. However, it has to be taken into account, that this lowest dose group included only small numbers of subjects in both parts.

- **Long-term exposure**

In Part II, in the subgroup of patient with age ≥ 6 years, the majority of subjects reported a TEAE in similar SOCs to those in Part I. The incidence was generally higher in the lower dose group (< 20 mg/kg/day) compared to ESL ≥ 20 mg/kg.

The TEAEs reported by most subjects ≥ 6 years in the subgroup ≥ 20 mg/kg/day in Part II were: headache (17.3%), somnolence (11.5%), vomiting (9.6%), pharyngitis (9.6%), tonsilitis (9.6%) gait disturbance (7.7%) and pharyngotonsillitis (7.7%) in the subgroup 20-<30 mg/kg/day, and seizure (11.4%), respiratory tract infection (9.5%), vomiting (7.6%), nasopharyngitis (7.6%), respiratory tract infection viral (6.7%) and headache (5.7%) in the subgroup 30 mg/kg/day.

In Part II, nervous system disorders remained the SOC with the highest percentage of subjects ≥ 6 years reporting possibly related TEAEs (9.8% of subjects). The most common possibly related TEAEs in dose groups ≥20 mg/kg/day were somnolence (3.8%) and seizure (3.8%).

Long-term data gathered from open-label extension up-to a period of 72 months exposure to ESL (corresponding to 342.2 persons-years of treatment) indicates a similar safety profile as in the double blind part.

- **AEs of special interest: Neurological AEs**

In the integrated Phase 2/3 paediatric studies at least 1 neurological TEAE was reported for 31.9% of total ESL subjects and 26.5% of placebo subjects during Part I and by 26.3% of subjects during Part II. The most common neurological TEAEs reported in both treatment groups during Part I and during Part II were convulsion, headache (11.8% ESL, 7.9% placebo) and somnolence (9.2% ESL, 4.8% placebo). These were also the most common neurological TEAEs reported in the different age groups (all >3%), except for the 2 to 5 years group during Part I, which had a higher incidence of ataxia (4.2% [2 patients] ESL, 0% placebo) and a lower incidence of headache (2.1% ESL [1 patients], 0% placebo).

A total of 21.1% of subjects reported at least 1 neurological TEAE during Parts III to V of Study 305 and the most common reported events were the same as in the integrated paediatric studies: convulsion (18 subjects [11.8%]), headache (12 subjects [7.9%]), and somnolence (3 subjects [2.0%]).

Serious adverse event/deaths/other significant events

Serious TEAEs during Part I of the Phase 2/3 paediatric studies were generally low. There was a higher incidence of subjects reporting serious TEAEs in the integrated paediatric studies (8.4% ESL subjects, 6.3% placebo subjects in Part I, and 9.4% ESL subjects in Part II) compared to the integrated adult studies (3.7% ESL subjects, 2.1% placebo subjects). Convulsion was the most common serious TEAE reported in the ESL and placebo groups in the integrated paediatric studies, while ataxia was the most common in the integrated adult studies (total ESL group only).

Most of the serious TEAEs reported by ESL subjects in the 6 to 11 years and the 12 to 18 years age groups were in the SOC nervous system disorders, in contrast to the 2 to 5 years age group with TEAEs belonging to the SOC infections and infestations.

The most common serious TEAEs reported by total ESL subjects during Part I were pneumonia among subjects 2 to 5 years (3.9% of subjects), and convulsion (3 ESL subjects versus 4 placebo subjects) which was reported by subjects in the 6 to 11 years (2.7%) and 12 to 18 (2%) years age groups. Status epilepticus occurred in 4 ESL subjects and in no placebo subjects.

Serious neurological TEAEs were reported for 3.8% of total ESL subjects and 3.7% of total placebo subjects during Part I and convulsion was the only serious neurological TEAE reported by >1 subject in any treatment group (3 subjects [1.3%] in the total ESL group and 4 subjects [2.1%] in the total placebo group). During Part II, serious neurological TEAEs were reported for 3.8% of subjects and convulsion (9 subjects [2.4%]) and epilepsy (2 subjects [0.5%]) were events reported for >1 subject. Serious neurological TEAEs were reported for 3.3% of subjects during Parts III to V and convulsion and status epilepticus were the only serious neurological TEAEs reported by >1 subject (2 subjects [1.3%], each).

In Study 202, there were 2 subjects with serious TEAEs of worsening of epilepsy (MedDRA lowest-level term: seizures) during the 30 mg/kg/day treatment period.

A total of 3 deaths occurred during the clinical development programme of ESL in children and adolescents, all in study 305. Two subjects died in Part I of the study: 1 ESL subject (4 events – convulsion, brain oedema, and bronchopneumonia and brain herniation – all led to death) and 1 placebo subject (asphyxia, age group 2 to 5 years). One ESL subject (age group 6 to 11 years) died during Part III from bronchopneumonia (study 305 Parts III to V). None of the deaths was considered related to study medication by the investigator.

Laboratory findings

There were no integrated analyses of clinical laboratory data.

- Study 305

No clinically relevant findings were seen in the analysis of vital signs, height, weight, BMI, head circumference, sexual maturation assessment, and electrocardiogram (ECG).

The highest incidence of subjects with laboratory values considered clinically significant by the investigator was reported for gamma-glutamyltransferase (GGT):

In the double-blind part of study 305, 3 subjects in the ESL group (3/155=1.9%) experienced clinically significant increased GGT values and 1 in the placebo arm (1/149=0.6%). In the open label phases of the study, 13 subjects (13/260 =5.0%) in Part II and 15 subjects (15/152= 9.9%) in Parts III to V presented increased values. Amongst these clinically significant GGT values, 2 in Part II were reported as serious TEAEs (2/260 = 0.7%), both with high GGT levels at baseline. They were reported for 1 patient each in the previous (Part I) placebo and ESL group.

Overall, 22 patients had GGT values higher than the higher level of reference value in study 305. From those, 15 patients (68%) had already high levels at baseline, and 4 (26.6%) had an endpoint value which was lower than the one at baseline. Only 3 cases actually presented values which were higher at endpoint than at baseline. Incidence of increased GGT values was low (about 2%) in the paediatric population in the double blind part of the study. As for long-term exposure, increased values remained low in frequency (less than 10% of patients).

- Study 208

Overall, no substantial changes in haematology and biochemistry laboratory parameters were reported in either treatment groups and no TEAEs of hyponatraemia were reported. Likewise, the mean changes from baseline for vital sign parameters, body weight, height, and head circumference were not substantially different across visits for the placebo and ESL treatment groups.

In part I, a slight reduction in total and free T3 levels was observed in the ESL group but these changes were mostly within normal range. In the ESL group, there were some reductions in T4 (total and free) levels, with a number of these values falling outside of the normal range. One event of hypothyroidism was reported in the placebo group. In part II, a slight reduction in total and free T3 levels was observed in the previous double-blind ESL group but these changes were mostly within the normal range. In the previous double-blind ESL group, there were some reductions in T4 (total and free) levels, with a number of these values falling outside of the normal range. One event of autoimmune thyroiditis was reported in the previous double-blind ESL group.

In part I, 2 patients had shifts from normal to abnormal in ECG parameters at Visit 4; 1 patient in the placebo group had low height of T-waves and 1 patient in the ESL group had irregular sinus rhythm with arrhythmia that was deemed not clinically significant. One patient in the ESL group had an abnormal ventricular extrasystole during the tapering-off period. No other patients had changes from normal to abnormal during the study. In part II, 1 patient in the previous double-blind ESL group had an abnormal ventricular extrasystole that started during the tapering-off period. No other patients had ECG changes from normal to abnormal during the study.

Safety in special populations

Study 208 investigated the effects of ESL on cognitive function in children with partial onset seizures (see section 2.5.2.2. for a summary fo the study results). The study outcome has previously been assessed (EMEA/H/C/000988/II/0041) and the CHMP concluded in relation to safety as follows:

Although non-inferiority was not demonstrated, ESL does not appear to have negative consequences for attention, information processing and working memory or episodic memory in the longer term in patients aged 6 to 16 years. The results obtained in the study do not substantially justify an extension of indication. Thus, more confirmatory data are necessary. The adverse event profile was consistent with previous data.

Safety related to drug-drug interactions and other interactions

No analyses on potential drug-drug interactions were conducted in paediatric subjects. Drug interaction studies, which were conducted in healthy adult subjects to investigate the effect of ESL on the PK of the AEDs and other

drugs and to investigate the safety and tolerability of co-administration, were reviewed in the context of the initial marketing authorisation application.

Discontinuation due to adverse events

In part I of study 305, study treatment was discontinued due to a TEAE by 7 patients (5.2%) in the ESL group and 3 (2.3%) in the placebo group. The only TEAE leading to treatment discontinuation reported more than once overall was convulsion (1 patient [0.7%] ESL, 3 patients [2.3%] placebo).

In part I of study 208, a total of 5 patients of the ESL group had TEAEs that led to discontinuation of study drug including 2 patients who experienced cutaneous events, which were considered potentially related to study drug (moderate rash, definitely related and mild allergic dermatitis, probably related).

In Study 202, the only TEAEs leading to discontinuation of study medication were the 2 serious TEAEs of seizures in 2 subjects during the ESL 30 mg/kg/day treatment period.

Overall, in the integrated paediatric studies, there was a lower incidence of TEAEs leading to discontinuation (5.5% of total ESL subjects, 1.6% of placebo subjects in Part I and 4.0% of ESL subjects in Part II) compared to the integrated adult studies (15.3% ESL subjects, 6.6% placebo subjects). The most common TEAEs leading to discontinuation of study medication in the integrated paediatric studies were dermatitis allergic, rash and convulsion. In the integrated adult studies, the most common TEAEs leading to discontinuation were dizziness, nausea, vomiting and ataxia.

Post marketing experience

Zebinix has been approved in the EU via Commission Decision in April 2009 as adjunctive therapy in adults with partial onset seizures with or without secondary generalisation. At the time of the submission of this application, ESL tablets were authorised for marketing (under the trade names of Zebinix, Exalief or Aptiom) in 43 countries including all the countries of the European Economic Area. Zebinix is marketed in 19 countries (Austria, Denmark, France, Germany, Iceland, Norway, Sweden, United Kingdom, Ireland, Greece, Czech Republic, Finland, Italy, Slovakia, Spain, Portugal, Malta, Cyprus and Albania) and Aptiom is marketed in the United States of America and in Canada. Exalief is authorised in 3 countries (Russia, Belarus and Ukraine) and marketed in Russia since March 2015.

Subject exposure to marketed Zebinix, Exalief or Aptiom was estimated on the basis of worldwide ex-factory sales for the period from 21-Apr-2009 until 31-Mar-2015. During this period, ex-factory cumulative amounts reached a total of 27,168,347 Units (1 unit = 1 tablet) sold and delivered in 22 countries, representing 905,611.6 patient-months of exposure.

The worldwide post-marketing safety experience for ESL is reflected in the Periodic Safety Update Reports (PSURs). The most recent PSUR for Zebinix covering the period from 22-Oct-2014 to 21-Oct-2015 concluded in May 2016. The Pharmacovigilance Risk Assessment Committee (PRAC) considered that the risk-benefit balance of medicinal products containing ESL remains unchanged and therefore recommends the maintenance of the marketing authorisation.

2.6.1. Discussion on clinical safety

The main basis for the safety assessment in support of this application was an integrated analysis of the key phase 2/3 paediatric studies 208 and 305. The MAH furthermore provided analyses by age and dose as well as a comparative review of paediatric and adult data. Overall, the safety data provided by the MAH were considered

sufficient and robust enough to conclude on the safety profile of ESL when used in children aged more than 6 years with refractory POS.

No age or dose specific safety concern was identified based on the available data that would have emerged as a new issue with the use of Zebinix. In many aspects, the safety profile of ESL in the paediatric population resembled the one in adults. Similar to the findings in adult studies, a dose-dependend trend in the incidence of possibly related TEAEs was observed and the most commonly reported related TEAEs were somnolence, vomiting, dizziness and diplopia. However, some safety issues including somnolence, vomiting, and diarrhoea, are assumed to have different implications for children and adolescents.

AEs of vomiting and diarrhoea may represent possibly greater risks in children, in whom fluid losses may lead more rapidly to situations of volume depletion and dehydration as compared to adult patients. Compared to adults, vomiting was reported at a similar incidence in the paediatric studies (6.5% in adults versus 7.1% in children treated with ESL) and diarrhoea was reported at a lower incidence (2.4% in adults and 1.6% in children treated with ESL). Considering the overall low reporting rates (lower than placebo in the case of diarrhoea), the fact that no dose-relationship was observed, and that the incidence was similar or lower compared to the adult population, overall no increased risk was identified for the paediatric population. Both vomiting and diarrhoea were already reflected in the product information as common ADRs. Details on the safety findings in the paediatric population have been included in section 4.8 of the SmPC and no further update was considered necessary by the CHMP.

As for somnolence, this AE has in fact been reported at a lower incidence in paediatric subjects treated with ESL compared to adults (9.2% versus 13.3%) and thus no increased risk for the paediatric population was inferred. Somnolence is identified as a very common event in the SmPC of Zebinix, with an incidence above 10%. A warning is included in the SmPC, for potential increased occurrence of accidental injury associated with somnolence or dizziness. No further amendments were considered necessary by the CHMP.

Analyses by age groups showed that te highest number of AEs has been reported in the youngest group (2 to 5 years of age), mainly due to TEAEs within the SOC of infections and infestations, but also for skin and subcutaneous tissue disorders. This issue was not pursued as during the course of the procedure, the MAH decided to exclude children aged 6 and less from the proposed extended target population due to differences in PK, the effective dose range and poor efficacy observed in the clinical trial 305 (see sections 2.4. and 2.5. for details).

When compared to adults, a higher incidence of SAEs has been reported in the paediatric studies, mainly consisting of convulsions. However, overall, serious TEAEs occurred at a low incidence, without specific pattern in single subjects only and in accordance with the known safety profile of ESL. The number of deaths (3) reported from the ESL paediatric studies was not higher as compared to other studies conducted in patients with epilepsy. It was furthermore considered unlikely that the cases deaths were related to study medication.

The following TEAEs were found to occur more frequently in paediatric patients compared to adults: convulsions (7-times higher), pyrexia (6-times higher) and all PTs under the SOC of infections and infestations. However, within the paediatric studies, these events occurred at similar (pyrexia) or lower (convulsions as well as infections and infestations) rate in the placebo group compared to ESL. For this reason, a correlation of AEs of convulsion to ESL seemed unlikely and events may have been more probably related to the underlying disease. Infections occur usually rather frequent in (smaller) children and thus a higher reporting rate compared to adults is not surprising and may not be attributed to ESL.

TEAEs leading to discontinuation were higher in the paediatric ESL group than for placebo and also for paediatric patients versus adults. However, when comparing this finding to other studies with AEDs, the rates were comparable and the issue was no longer pursued.

Two events of dermatitis allergic (0.8%) were reported in paediatric patients receiving ESL (compared to none in the placebo group). This event has previously not been reported in adults, although cutaneous adverse reaction are known to occur under treatment with ESL. Dermatitis allergic was added to SmPC section 4.8 as an uncommon ADR.

With regards to laboratory findings, the incidences of cases of GGT increased and T4 decreased were higher in the paediatric group when compared to adults. Additional analyses presented by the MAH however suggest no relevant safety issue neither with the use of ESL and the incidence of impaired thyroid function (T4 increased) nor the increased GGT values. Hypothyroidism and liver disorders were already included in the SmPC as adverse reactions. No further changes to the safety information were considered necessary.

Finally, long-term data gathered from the open-label extensions of the paediatric studies up-to a period of 72 months, corresponding to an exposure to ESL of 342.2 persons-years of treatment, indicate a similar safety profile as in the double blind part of the studies. While the effects of ESL on cognition have been evaluated in study 208 for up to 4 years, suggesting that ESL has no negative consequences for attention, the available data were not considered sufficient to resolve uncertainties of long term effects on brain development, learning and intelligence. Furthermore, there was insufficient data to confirm that ESL has no long-term effects on growth, endocrine function, puberty and childbearing potential in children. Continued routine observation in the post marketing phase will allow further monitoring of the long-term safety of ESL in children. Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children was included in the RMP as misssing information. No further measures were considered necessary by the PRAC and the CHMP.

The MAH also took the opportunity to correct the frequencies of the listed ADRs thrombocytopenia, leukopenia and pancreatitis from ‘rare’ to ‘not known’. Thrombocytopenia was moved to the frequency category “not known” since it has only been reported during the open-label phase of study 301 (adults). Leukopenia was similarly changed to the category “not known” since it was more common with placebo compared to ESL. However, it is a known class effect for AEDs like oxcarbazepine. Pancreatitis was only reported in the open-label phase of study 301 and is known to be very rare in general for the structurally related compound oxcarbazepine. Hence, the frequency category “not known” was considered more appropriate.

2.6.2. Conclusions on the clinical safety

ESL was generally well-tolerated when used as adjuvant therapy in the treatment of children with POS. The incidence of SAEs and discontinuations due to AEs was overall low although slightly higher in paediatric subjects compared to adults. There were no new major safety concerns arising from the paediatric clinical studies at the applied maintenance doses of 20 and 30 mg/kg/day. The safety profile of ESL in children older than 6 years was overall consistent with the known safety profile of ESL in adults.

The CHMP thus concluded that the safety data presented in this application were adequate to support the extension of the indication of Zebinix to adjunctive therapy in adults, adolescents and children aged above 6 years, with POS with or without secondary generalisation.

2.7. Risk Management Plan

The CHMP received the following PRAC outcome on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version V18 is acceptable.

The CHMP endorsed the Risk Management Plan version V18 including the following changes:

Safety concerns

Table 18 – Summary fo the Safety Concerns

Important identified risks	Hyponatremia Cutaneous adverse reactions
Important potential risks	Thyroid function changes INR and 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 plan

No further studies have been planned since the last update to the pharmacovigilance plan.

Risk minimisation measures

The 2 following missing information has been updated as follows:

Table 19 – Summary of Risk Minimisation Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Pediatric population (<= 6years of age)	ESL is not recommended for use in children aged 6 years and below, as the safety and efficacy of eslicarbazepine acetate has not yet been established. (in section 4.2 of the SPC)	None

	Studies BIA-2093-305 and BIA-2093-208 have been completed. PIP (P/0197/2013; EMEA-000296-PIP02-M04) is ongoing	
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

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The main changes to SmPC sections 4.1 and 4.2 were as follows (added text is shown in **bold**, deleted text as ~~strike-through~~):

Section 4.1

Zebinix is indicated as adjunctive therapy in adults**, adolescents and children aged above 6 years,** with partial-onset seizures with or without secondary generalisation.

Section 4.2

(…)

Paediatric population

Children above 6 years of age

The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg

Children with a body weight of 60 kg or more should be given the same dose as for adults.

The safety and efficacy of eslicarbazepine acetate in children ~~and adolescents~~ **aged 6 years and** below ~~18 years~~ has not yet been established. **Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.**

(...)

Switching preparations

Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

(...)

Changes to SmPC section 4.4 were related to QRD comments including removal of information on interactions with oral contraceptives and oxcarbazepine, for which section 4.5 was found more suitable. Section 4.5 was updated accordingly, whereby the current information on oral contraceptives was considered sufficient.

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

Furthermore, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representative of Spain.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

A full user test was performed at the time of the initial marketing authorisation. In updating the package leaflet, following the development of the oral suspension and new paediatric indication, the CHMP agreed that there was no need to perform a new readability test. Crucial information concerning safety and compliance has not been modified.

3. Benefit-Risk Balance

3.1. Therapeutic Context

ESL has been authorised in the EU/EEA via the centralised procedure by Comission Decision since April 2009 for the adjunctive therapy in adults with POS with or without secondary generalisation. The MAH has now completed a paediatric development programme with ESL and applied for an extension of the indication to to children aged 2 years and older. However, during the course of the procedure the age range was proposed to be limited to children aged more than 6 years. The MAH furthermore applied for the introduction of an oral suspension (50 mg/mL ESL) as a paediatric formulation.

3.1.1. Disease or condition

Epilepsy with POS is characterised by abnormal, excessive or hypersynchronous neuronal activity originating in a discrete area of the cerebral cortex, but which may later spread to involve both cerebral hemispheres causing secondary generalisation. Epileptic seizures can be treated with AEDs, aiming at achieving seizure reduction and

ideally seizure freedom. About 20-30% of epilepsy patients including those with POS are refractory and require treatment with a combination of 2 or more AEDs in order to control seizure activity. As recognised in the CHMP Epilepsy Guideline, partial epilepsies in children older than 4 years have a similar clinical expression to partial epilepsies in adolescents and adults. Efficacy of AEDs in the treatment of refractory POS, once established in adults and adolescents, can thus to some extent be extrapolated to children.

3.1.2. Available therapies and unmet medical need

Several AED treatment alternatives exist for POS, including carbamazepine, lamotrigine and many others. Development in children is often delayed as most new AEDs are first tested in the add-on treatment of adults with POS. However, approximately half of the epilepsies have an onset before the age of 18 years and the incidence is highest in infants and the elderly. There is thus a need for further treatment options for children to allow optimisation of individual therapy. Furthermore, in order to account for the special needs of paediatric patients, adequate pharmaceutical forms (i.e. liquid formulations) are needed.

3.1.3. Main clinical studies

Two clinical studies (208 and 305) have been conducted as main support for efficacy of ESL as adjunctive therapy in children with or without secondary generalization. Furthermore, efficacy of ESL in the add-on treatment of adults with refractory POS has previously been established based on the results of 3 pivotal trials (301, 302 and 303).

In the two main paediatric studies, ESL was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. Whereas in study 208 the target dose was 30 mg/kg/day, the initial target dose in study 305 was 20 mg/kg/day, which could be further titrated to 30 mg/kg/day only during the titration period. Study 208 recruited children aged 6 to 16 years whereas study 305 included children aged 2-18 years. Study 305 was designed as a confirmatory phase 3 efficacy and safety study; study 208 primarily aimed at investigating the safety of ESL with regards to its effect on cognitive function and all efficacy endpoints were secondary.

Finally, the application for the oral suspension was not supported by *in vivo* bioequivalence study data. Rather, the MAH proposed a bridging approach relying on studies previously conducted and assessed, to show comparable bioavailability between different pharmaceutical forms and clinical trial versus commercial formulations.

3.2. Favourable effects

With regards to the paediatric data, in study 208, LS mean reduction in standardised seizure frequency was significantly higher in children treated with ESL compared to placebo (-34.8% and -13.8, respectively, $p<0.001$). The percentage of 50% responders during the maintenance period was lower in the placebo group compared to ESL (25.0% and 50.6%, respectively, $p=0.009$). Subgroup analyses by age group (6-11 and 12-16 years) were consistent with the overall study results for both responder rate and relative change in standardised seizure frequency.

In study 305 (double-blind part I), both primary efficacy variables, the 50% response rate (30.6% for ESL versus 31.0% for placebo) and the relative change in standardised seziure frequency during the maintenance period (18.1% for ESL versus 8.6% for placebo) were similar in patients treated with ESL and placebo. No clinically relevant and/or statistically significant difference was seen in the overall study population. However, when the analysis population is limited to age stratum II and III (7-11 years and 12-18 years), 36/103 patients

(35.0%) in the ESL group compared to 29/96 (30.2%) in the placebo group were responders (p=0.4759). Also, LS mean relative change in the standardised seizure frequency from baseline to the maintenance period was higher in the ESL group than in the placebo group (-24.4% versus -10.5%, p=0.1040). While still not statistically significant, the results showed a numerical trend in favour of ESL over placebo. When limiting the efficacy analyses of study 305 further to both age strata II+III and patients titrated to the maximum dose level (30% of the patients), the 50% response rates were found to be 48.3% in patients receiving ESL and 30.6% in the placebo group (p=0.1514) and the between-treatment difference in relative reduction of standardized seizure frequency became statistically significant (LS mean difference: 31.9, p=0.0478).

As for the oral suspension, comparable bioavailability has previously been shown for (i) the commercial tablet formulation and the clinical trial tablet formulation and (ii) the clinical trial tablet formulation and the clinical trial oral suspension formulation. Similarity of the clinical trial oral suspension formulation and the commercial oral suspension formulation was furthermore supported by tests showing comparative dissolution profiles. Overall, the PK data and additional simulations presented by the MAH showed that differences in the composition of the formulations, the change of dosage form or concomitant administration of food had no major effect on bioavailability.

3.3. Uncertainties and limitations about favourable effects

Uncertainties in relation to the efficacy of ESL arose from the failure of study 305 and the inconsistent results of study 305 and 208. Comparison of the two studies indicated some heterogeneity but no single baseline characteristic or demographic factor was shown to have consistently influenced the study outcome towards a larger effect sizes in study 208 compared to study 305 or vice versa. However, PK analyses revealed that exposure to ESL at a given dose was lower in younger children (2-6 years) compared to older children (7-18 years). According to simulations based on a population PK model, a minimum daily dose of 27.5 mg/kg/day is necessary in the group of 2-6 year olds to match the exposure achieved with 20 mg/kg/day in the other two age groups. Doses for 2-6 year old children to match exposure with 30 mg/kg/day would obviously exceed this dose which was the highest explored dose in the clinical trials. Based on these data, it is plausible that inclusions of the youngest age group of 2 to 6 year olds and underestimation of the efficacious dose range in this population have contributed to the failure of study 305.

To further support this argument, the MAH conducted several subgroup and post-hoc analyses. These analyses, while supportive, were considered by the CHMP to be of limited interpretability due to small sample sizes (subgroups of subgroup analyses) and the post-hoc nature of some of the analyses. With regards to the results from study 305, it should also be noted that the therapeutic effect in the placebo group was larger than expected, while that in the ESL group was lower than expected. The MAH suggested that difficulties in recognising or identifying simple partial seizures in children, particularly for the 2-6 years group, could have been a factor contributing to the high variability in baseline seizure frequency and study outcome and to the high pacebo response rate.

The main difference between studies 208 and 305 that could explain the inconsistent results of the two studies appeared to be the different dosing regimens. Even if only children > 6 years from study 305 (stratum II+III) were considered, the treatment effect of ESL observed in study 305 was substantially lower than in study 208. However, while the target dose in study 208 was 30 mg/kg/day (83% of ESL patients were titrated to this dose), the target dose in study 305 was 20 mg/kg/day (only 39% of patients were titrated to 30 mg/kg/day). Analyses by dose showed a trend for a higher efficacy of the 30 mg/kg/day dose in study 305, but again the results of this post-hoc analysis of a small subgroup should be interpreted with care, in particular analyses according to dose

are difficult to interpret in a study involving titration according to efficacy as comparisons are not based on randomised groups.

Concerns in relation to efficacy and dosing in the age group of 2-6 year old patients were not further pursued as during the course of the procedure the MAH proposed to limit the age range in the indication to children older than 6 years. This was agreed by the CHMP given the uncertainties arising from the observed PK differences across age groups and the poor efficacy results for this age group in study 305.

As for the data presented to support approval of the oral suspension formulation, some uncertainties remained with regards to the full interchangeability of the tablets and the oral suspension in absence of a relative bioavailability study comparing the two commercial formulations. While no problem was foreseen in patients being started on Zebinix, since the optimum dose for this product is titrated individually, uncertainties remained if patients taking one of the two formulations could be switched to the other at the same dose level. Therefore, caution is advised when switching pharmceutical forms. The CHMP furthermore recommended for the MAH to conduct a relative bioavailability study comparing the commercial formulations of the tablets and the oral suspension.

3.4. Unfavourable effects

The overall incidence of TEAEs in the integrated analysis of paediatric studies was 66.4% (158/238) for ESL treated subjects and 65.1% (123/189) for placebo subjects. The most common TEAEs reported with ESL were headache (11.8% ESL, 7.9% placebo), somnolence (9.2% ESL, 4.8% placebo), vomiting (7.1% ESL, 4.8% placebo), nasopharyngitis (6.7% ESL, 7.9% placebo) and convulsion (6.7% ESL, 9.5% placebo).

More paediatric patients in the ESL group discontinued as a consequence of AEs (1.6% placebo, 5.5% ESL). SAEs occurred in 6.3% of placebo treated patients and 8.4% of patients in the ESL group. Three deaths occurred; two during the double-blind study phase (one each in the ESL and the placebo group and one during the open-label extension of study 305). None of the cases was considered related to study medication.

Overall, the safety profile of ESL in the paediatric studies was comparable to the known safety profile in adults and no new safety issue arose from the paediatric study data. Similar to the findings in adult studies, a dose-related trend in the incidence of possibly related TEAEs was observed in children.

With regards to important identified risks in the RMP, subcutaneous tissue disorders were reported by 9.2% (ESL) and 6.9% (placebo) of the patients in the paediatric studies. For hyponatraemia, no case was reported in the paediatric studies.

In the age group from 2 to 5 years of age, the most common possibly related TEAE observed in more than two patients treated with ESL were somnolence (10.4%); in patients aged from 6 to 11 years treated with ESL the most common possibly related TEAEs were diplopia (9.5%) and nausea (3.2%); in the age group from 12 to 18 years these were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). Otherwise, some age-related differences in the incidence of TEAEs have been detected. Infections and infestations as well as skin and subcutaneous tissue disorders were found to be more frequent in the younger age group (2-6 years), whereas the age group above 6 years of age was more affected by TEAEs related to nervous system disorders.

3.5. Uncertainties and limitations about unfavourable effects

Slightly more TEAEs were reported for the youngest age group compared to the older patient groups. This issue was not pursued as during the course of the procedure, the MAH decided to exclude the youngest age group

from the proposed extended target population due to unceratinties relating to PK and the effective dose range as well as poor efficacy observed in the clinical trial 305.

Some differences in the incidence rates for adults and paediatrics were observed. The following TEAEs were found to occur more frequently in paediatric patients compared to adults: convulsions (7-times higher), pyrexia (6-times higher) and all PTs under the SOC of infections and infestations. However, within the paediatric studies, these events occurred at similar (pyrexia) or lower (convulsions as well as infections and infestations) rates in the placebo group compared to ESL. With regards to convulsion, a correlation to the drug itself seems unlikely and events may be more probably related to the disease to be treated. Infections occur usually rather frequent in (smaller) children per se and may not be attributed to ESL.

Long-term data from open-label extension of the paediatric studies up-to a period of 72 months indicate a similar safety profile as in the double blind study parts. Overall, the data were not considered sufficient to confirm that ESL has no detrimental effects on brain development, learning and intelligence. Likewise, there was insufficient data on long-term effects like effect on growth, endocrine function, puberty and childbearing potential in children. These long-term effects were included as missing information in the RMP. Continued routine observation in the post marketing phase was considered sufficient to monitor long-term safety of ESL in children.

3.6. Effects Table

Effects Table for Zebinix for adjunctive therapy of children and adolescents above 6 years with POS with or without secondary generalisation

Effect	Short Description	Unit	ESL	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Seizure reduction: 50% responder rate	Rate of patients with a reduction of seizures of 50% or more	%	35.0%(1) 48.3%(2) 50%(3)	30.2%(1) 30.6%(2) 25%(3)	Study 305(1, 2): Differences not statistically significant. Strata were defined and analysed post-hoc. Results from study 305 in the total population suggest no difference between active and control arm. Based on PK and comparative exposure analyses, the results were possibly driven by stratum I (2-6 years) due to high variability and under-dosing in this age group. Study 208(3): Efficacy was a secondary objective, limited number of patients.	CSRs of study 305 and 208, see also section 3.3.5 of this report
Unfavourable Effects						
Cutaneous adverse reactions	Incidence of cutaneous TEAEs **paediatrics** / adults	%	**9.2** / 5.5	**6.9** / 6.1	Low number of subjects included in paediatric studies. The limited size of the paediatric safety database precludes the	Paediatrics: (i) Integrated paediatric analysis (studies 305

Effect	Short Description	Unit	ESL	Placebo	Uncertainties/ Strength of evidence	References
Hyponatraemia	Incidence of TEAEs of hyponatraemia (including *blood sodium decreased* and *hyponatraemia*) in **paediatrics** / adults	%	**0** / 1.9	**0** / 0	detection of rare events and precise frequency estimations.	and 208) (ii) Safety sets for studies 305 and 208 Adults: (i) Integrated adult analysis (Part 1 of studies 301, 302, 303, 304, 201) (ii) Safety sets of studies 301, 302, 303, 304, 201
Nervous system disorders	Incidence of TEAE - somnolence **paediatrics** / adults - convulsion **paediatrics** / adults	%	**9.2** / 13.3 **6.7** / 0.9	**4.8** / 7.9 **9.5** / 1.3		

Abbreviations: GI=gastrointestinal; NS=Nervous System; PK=Pharmacokinetic; PD=Pharmacodynamic; SSF= standardised seizure frequency; ESL: eslicarbazepine

(1) Study 305 age strata II+III including paediatric patients aged 7-17 years
(2) Study 305 age strata II+III including paediatric patients aged 7-17 years receiving ESL 30 mg/kg/day
(3) Study 208 including paediatric patients aged 6-16 years.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy of ESL in the treatment of POS has previously been demonstrated in adult patients. Given that disease expression of partial epilepsies is similar in adults, adolescents and children, the CHMP was of the view, that, in line with the CHMP Epilepsy Guideline, extrapolation of the established efficacy of ESL in adults to children was possible, , provided that a suitable dose range can be established.

With regards to the paediatric data, the CHMP considered that, while the reason for the failure of study 305 cannot be finally explained, factors such as recommending the lower dose of 20 mg/kg/day as the target dose, a high response to placebo, and including children aged 2-6 years, for whom the tested dosage appeared to be too low, may have played a role. Because of the uncertainties arising from the observed decreased exposure and the poor efficacy results for the youngest age group of 2 to 6 year olds, the CHMP was of the view that the indication should be restricted to patients older than 6 years. For this restricted new target population, subgroup analyses excluding stratum I (2-6 years) in study 305 were considered relevant, although conducted post-hoc. Within the remaining age range (7-18 years), a beneficial trend in favour of ESL was observed. Results achieved with the 30 mg/kg/day ESL dose in this age range indicated a clinically relevant effect for ESL for both the 50% responder rate (48.3% for ESL versus 30.6% for placebo) as well as for the relative change in standardised seizure frequency (37.2% for ESL versus 5.2% for placebo), although only the between treatment difference for the reduction in standardised seizure frequency reached statistical significance. Efficacy results obtained in study 208, although being only the secondary study objective, were also of a magnitude considered clinically relevant (LS mean difference in seizure frequency of -20.99 and 25% higher 50% responder rate in ESL compared to placebo subjects) and comparable to the effects seen in the adult study population.

Overall, the available study data did not provide convincing support for efficacy of the 20 mg/kg/day dose. However, a small difference between ESL and placebo in the 20 mg/kg/day dose subgroup does not mean that ESL is not efficacious at all at this dose level and thus the 20 mg/kg/day could be a therapeutic option at least

in some patients. Furthermore, it was shown that comparable exposure to eslicarbazepine as well as comparable $c_{av,ss}$ and $c_{av,min}$ is achieved with paediatric ESL doses of 20 and 30 mg/kg/day and the adult doses of 800 and 1200 mg/day, respectively. Both 800 mg and 1200 mg/day have previously been shown to be effective in adults and based on these data, extrapolation of efficacy was considered possible for children > 6 years. Based on these results, it was agreed that paediatric patients can be titrated up to a dose 30 mg/kg/day according to treatment response.

Clinical safety in paediatric patients was broadly in line with the known safety profile in adults. Minor deviations were observed, i.e. in the incidence of convulsions and infections, shown to be more pronounced in paediatrics, in particular in the youngest patients, compared to adults. However, since TEAEs in regard to convulsions have been reported more frequently in paediatric subjects on placebo compared to ESL, a correlation to the drug itself seemed unlikely and events may have been more probably related to the underlying disease. Infections occur usually rather frequent in (smaller) children per se and may not be attributed to ESL. Overall, no safety issues have been identified that would preclude the use of ESL in children or adolescents. Routine post marketing monitoring will help to detect any possible long-term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential.

Finally, with regards to the oral suspension, the available PK data indicated that ESL has a low potential for formulation effects. Differences in the composition of the formulations, the change of dosage form or concomitant administration of food had no major effect on bioavailability and no clinically relevant impact of a switch from oral suspension to tablets was seen in study 305.

3.7.2. Balance of benefits and risks

In order to extrapolate clinical efficacy of ESL in the treatment of refractory POS in adults to children and adolescents, the effective and safe dosage range needs to be established. This was not possible for children aged 6 years and less on the basis of the evidence provided by the MAH and consequently, the CHMP considered the benefit-risk balance negative in this age group.

For children older than 6 years, while the available data provided only limited support for efficacy of the 20 mg/kg/day dose, since comparable exposure was shown for the proposed paediatric ESL maintenance doses (20 and 30 mg/kg/day dose) and the established adult maintenance doses (800 and 1200mg/day), the CHMP considered that extrapolation of efficacy was possible and that the proposed dose range of 10 mg/kg/day (starting dose) to 30 mg/kg/day was justified. Given that the safety profile in the paediatric population was largely in line with the established profile in adults, the CHMP concluded that the benefits of ESL as adjunctive therapy in adolescents and children aged above 6 years, with POS with or without secondary generalisation outweight the risks. The benefit-risk balance was thus favourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk balance of Zebinix is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zebinix as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation is favourable and therefore recommends the extension of the marketing authorisation for Zebinix 50 mg/ml oral suspension subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- ***Risk Management Plan (RMP)***

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0015/2015 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		**Type**
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	II

Extension of indication to add treatment of adolescents and children aged above 6 years (adjunctive therapy in patients with partial-onset seizures with or withour secondary generalisation).

Consequently, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes and implement the latest QRD template in the SmPC, Annex II, labelling and Package Leaflet.

Furthermore, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representative of Spain.

The application included a revised RMP version 18.0.