European Medicines Agency

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CHMP ASSESSMENT REPORT

FOR

Exalief

International Nonproprietary Name: eslicarbazepine acetate

Procedure No. EMEA/H/C/000987

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant BIAL - Portela & Ca, S.A. submitted on 03 March 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Exalief, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 27 June 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier, composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 14 December 2006 and 21 June 2007. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Karl Broich** Co-Rapporteur: **Martin Votava**

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 03 March 2008.
- The procedure started on 26 March 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2008. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 21-24 July 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 November 2008.
- During the CHMP meeting on 15-18 December 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 January 2009.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 February 2009.
- During the meeting on 16-19 February 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation for Exalief on 19 February 2009. The applicant provided the

letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 February 2009.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Epilepsy is a chronic disease that requires long-term treatment. The World Health Organisation (WHO) estimates that around 50 million people in the world have epilepsy at any one time, which is roughly 1% of the world population. Recent studies have shown that up to 70% of newly diagnosed children and adults with epilepsy in both developed and developing countries can be successfully treated (i.e. their seizures can be completely controlled for several years) with AEDs. However, despite a broad range of AEDs available on the market, roughly 30-40% of patients with epilepsy are uncontrolled with available treatment and a further 25% suffer from significant adverse effects [CPMP/EWP/566/98 rev1]. This is due to poor response and to the associated toxicities of available AEDs.

About the product
Exalief tablets contain the new active substance eslicarbazepine acetate, which was designed to constitute a third generation, single-enantiomer member of the long-established family of first-line dibenz[/b,f/]azepine anti-epileptic drugs represented by carbamazepine (CBZ, first-generation) and oxcarbazepine (OXC, second generation). The product is available in strengths of 400 mg, 600 mg, and 800 mg. The proposed indication is "Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation". The use of ESL in children will be applied for after the Marketing Authorisation Application (MAA) for the adult indication has been granted.
The recommended dose is 800 mg once daily. New patients should be initiated on 400 mg once daily for one week before up titration. Based on individual response, the dose may be increased to 1200 mg once daily. Dose adjustments are recommended based on renal function, otherwise no dose recommendations for special populations are proposed.

Eslicarbazepine acetate (ESL) is a prodrug of eslicarbazepine, which is the drug entity responsible for the ESL pharmacological effect. Preclinical experiments suggest that both ESL and eslicarbazepine competitively interact with site 2 of the inactivated state of a voltage-gated sodium channel (VGSC), preventing its return to the active state and repetitive neuronal firing. The precise mechanism by which ESL exerts its antiepileptic effects remains to be fully elucidated.

The development programme/Compliance with CHMP Guidance/Scientific Advice
The clinical development programme included 22 Phase I studies in healthy subjects or special populations, 2 Phase II studies and 3 Phase III studies. In addition, 3 Phase II studies were performed in adults with bipolar disorder. In these studies, ESL at any dose was administered to a total of 1694 subjects: 558 non-epileptic adults, and 936 adults and 31 children with refractory partial epilepsy and 172 adults with bipolar disorder. All ESL doses were given orally in the clinical studies, either as tablets or as a suspension.

A scientific advice for this product was given by the CHMP 2006-12-14 Scientific recommendations have been given by Sweden in 2006. A paediatric development programme has been announced, but not submitted yet. This is acceptable as at the day of submission of the application the inclusion of a PIP was not formally mandatory. However, the applicant declared that the use of ESL in children will be applied for after the Marketing Authorisation Application (MAA) for the adult indication has been granted.

2.2. Quality aspects

Introduction

Exalief is presented as tablets containing 400, 600 or 800 mg of eslicarbazepine acetate (active substance). The excipients used in the formulation of the finished product are well known excipients such as povidone K29/32, croscarmellose sodium and magnesium stearate.

Exalief 400 mg tablets are white circular biconvex, engraved 'ESL 400' on one side and scored on the other side. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

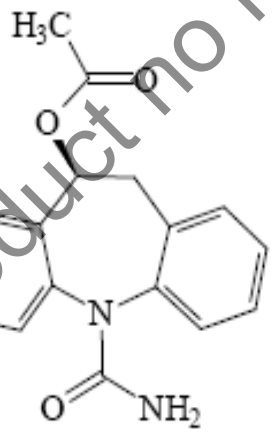
Exalief 600 mg tablets are white oblong, engraved 'ESL 600' on one side and scored on the other side. The tablet can be divided into equal halves.

Exalief 800 mg tablets are white oblong, engraved 'ESL 800' on one side and scored on the other side. The tablet can be divided into equal halves.

Tablets are packaged in Alu/Alu or Alu/PVC blisters placed into cardboard boxes. Tablets of 600 mg and 800 mg strengths may be packed in HDPE bottles with polypropylene child resistant closure and placed into cardboard boxes.

Active Substance

The active substance is chemically designated as (S)-10-Acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (Chemical Name) and has the following structure:



Eslicarbazepine acetate has one chiral centre, so it is optically active. It is synthesized as the S-enantiomer with the (S)-configuration at C_{10}. It is white to off-white, non-hygroscopic, odourless crystalline solid. The solubility of eslicarbazepine acetate in organic solvents at a temperature between 15 and 25 ºC, and in aqueous buffer solutions with a pH between 1.20 and 7.40, at 37 ± 1 ºC, has been determined according to Ph Eur and USP classification. Under physiological conditions eslicarbazepine acetate is a non ionisable compound. Hydrolysis of the ester group occurs at low and high pH (1.2 and 10, respectively). It melts at 184 – 187 ºC, with decomposition.

No polymorphs were observed by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot stage microscopy, spectroscopy (FT-Raman and FT-IR), and moisture sorption/desorption analysis.

- Manufacture

The synthesis of the drug substance consists of five steps followed by a micronisation step. Four intermediates are isolated during the manufacture of eslicarbazepine acetate. In process controls include tests for diastereomeric and enantiomeric purity.

The proposed manufacturing process has been adequately described, critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

The structure of eslicarbazepine acetate has been confirmed by elemental analysis (C, H and N), and spectroscopic analyses (IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry). Typical spectra of eslicarbazepine acetate have been provided and analysed in detail

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.

- Specification

The drug substance specification includes tests for appearance particle size distribution (laser diffraction), identification (IR and HPLC), assay (HPLC), purity, including enantiomeric purity (HPLC), water content (Karl Fisher), melting point, residue on ignition, heavy metals, residual solvents (GC), microbial purity and sulphated ash.

All non-compendial analytical methods have been validated. The HPLC methods for assay and purity have been validated for specificity (selectivity), linearity, accuracy, precision (system precision, analysis repeatability, intermediate precision), recovery, LOD, LOQ, stability of solutions, and robustness. Forced degradation studies with eslicarbazepine acetate were performed under several stress conditions e.g. by treatment with heat, under acidic and alkaline conditions as well as under oxidizing conditions to justify the specificity of the method for purity.
The GC method for residual solvents has been validated regarding specificity (selectivity), linearity, accuracy, precision (system precision, analysis repeatability, intermediate precision), LOD, LOQ, stability of solutions, and robustness. Suitable validation data for the water determination (Karl-Fischer) and the particle size test method have also been provided.

In general analytical methods have been sufficiently validated and are suitable to control the quality of the drug substance.

Batch analysis data on 6 batches from the proposed manufacturing sites has been provided. In addition information about all eslicarbazepine acetate batches used in non-clinical, clinical and stability studies has also been given. All results are with specifications and show batch-to-batch and site-to-site consistency.

- Stability

Stability studies have been performed on three consecutive production scale batches of eslicarbazepine acetate at real time (25° C/60 % RH) and intermediate conditions (30° C/65 % RH). The same batches have been tested at accelerated conditions (40° C/75 % RH)) for 6 month. The specification and the analytical methods used were the same as those proposed for control of the drug substance.

The stability data showed that the drug substance is stable under real time, intermediate and accelerated storage conditions. All parameters tested in the stability studies remained within the specified limits over the period tested. There was no evidence of any significant change or degradation under any of the conditions.
A photostability study has been performed on one batch of the drug substance. The protocol was in line with the Note for Guidance on Photostability Testing of New Active Substances and medicinal Products.

The stability studies confirmed the proposed re-test period, when the drug substance is stored in the proposed containers.

Medicinal Product

- Pharmaceutical Development

In order to assure the convenience of administration and precision of dosage the drug product has been developed as immediate-release tablets for oral administration. Compatibility between eslicarbazepine acetate and excipients in the formula intended for marketing as well as some of the excipients used in clinical trial formulations has been investigated in compatibility studies. No major incompatibilities have been determined. In early development phase different formulations were used in clinical trials. Comparative studies were performed to demonstrate in-vitro and in-vivo equivalence between these formulations and the formulation intended for marketing. Obtained results confirmed that formulations were comparable.

The impact of different particle sizes of the active substance on dissolution has been investigated during the development phase. As the active substance has low aqueous solubility the particle size is reduced by milling during the manufacture in order to increase surface area and consequently improve dissolution. Three active substance batches representing small, intermediate and large particle size within the specified range were selected for study and showed similar dissolution profiles. Moreover study comparing *in vitro* behaviour of tablets with active substance from different sources and different synthesis pathways has been carried out..

Data on the development of the dissolution method has also been provided. Initially a 'conventional' dissolution method had been selected with a single point specification and with standard pharmacopoeial conditions. 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. Sufficient discriminatory power could be demonstrated. However, during formulation development results from some formulations with different amounts of excipients in the tablet led to increased amplitude of variation of results. To avoid misleading out of specification results an alternative dissolution method has been developed. It has been shown, based on the performed experiments, that the method is able to discriminate among drug product lots that are found to have minor differences in the composition, hardness, moisture or manufacturing process. Dissolution method assures consistent product performance.

- Adventitious Agents

The drug product does not contain any substances with TSE/BSE risk. Magnesium stearate used in the formulation is of vegetable origin.

- Manufacture of the Product

A standard manufacturing process, which is direct compression of a dry blend, is utilised for the drug product manufacture. The drug substance is pre-mixed with excipients and the obtained pre-mix is wetted and then granulated. After drying the granulate is mixed with excipients and compressed.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

The robustness of manufacturing procedure for the proposed commercial formulation has been demonstrated by successful manufacture of several batches at a manufacturing scale. Extensive experience over the years demonstrates that the manufacturing process is well under control and a drug product of adequate quality within the approved specifications is obtained and a continuously high level of quality can be guaranteed.

- Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance (description), identification (HPLC), average weight, uniformity of dosage units, thickness, hardness, friability, water content (Karl Fisher), dissolution, assay (HPLC), degradation products (HPLC), microbial purity.

Analytical methods have been adequately described and validated for the intended use. The HPLC method for assay, identification, and degradation products has been validated with respect to solution stability, selectivity, LOD and LOQ, linearity, repeatability of the system, repeatability of the method, intermediate precision, accuracy, recovery, and robustness. The HPLC method used for the dissolution testing has been validated for solution stability, carryover, selectivity, linearity, repeatability of the system, repeatability of the test procedure, intermediate precision, accuracy, and robustness. The proposed two Karl Fisher methods (coloumetric and volumetric titration) for the water content have also been validated.

Results from several batches of 400, 600 and 800 mg tablets have been presented. The batch data comprises results both for the commercial formulation and for the batches of other formulations used in the pivotal phase III studies. Results for non-commercial batches have been provided as supportive information. Batch analysis results on 6 batches of the drug product (each strength) indicate satisfactory uniformity and compliance with the agreed specification.

- Stability of the Product

Two separate stability studies have been initiated, one study with pilot scale batches manufactured in the site intended for commercial manufacturing and in an alternative site used during the development. Both studies comprise tablets 400, 600 and 800 mg packaged in the three different packaging materials (Alu/Alu blisters, PVC/Alu blisters and HDPE bottles) intended for marketing. Three bulk batches of each of the tablet strengths were manufactured. Tablets from each bulk batch were then packaged in all three packaging materials, and were assigned with separate batch numbers. Batches have been stored under long-term (25 ±2 °C/60±5% RH), intermediate (30 ± 2°C/65±5 % RH), accelerated (40 ± 2°C/75±5 % RH) conditions.

The photostability study was performed according to ICH Q1B guideline which demonstrates satisfactory resistance to photodegradation under ICH conditions.

The applicant declared that the ongoing stability studies at both sites will be continued according to the stability protocols presented. Also first 3 commercial batches of each strength of will be placed on stability and the studies will follow the same principles outlined for the Registration batches.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 the clinic.

2.3. Non-clinical aspects

Introduction

Eslicarbazepine acetate (ESL) represents a third-generation, single enantiomer member of the well-known family of first-line dibenz[b,f]azepine antiepileptic drugs carbamazepine (CBZ, first generation) and oxcarbazepine (OXC, second generation). Although the precise mechanism of action is unknown electrophysiological studies indicate that both ESL and its active metabolites stabilize the inactivated state of voltage-gated sodium channels (site 2). Therefore, ESL is supposed to act as a voltage-gated sodium channel blocker.
The pharmacology studies have utilised ESL, eslicarbazepine, R-licarbazepine and OXC. In addition, the congener drug CBZ has been used as a comparator in some studies. In few studies the mixture of both enantiomers (eslicarbazepine + R-licarbazepine) were used.

GLP aspects

All safety and toxicity studies were conducted in GLP compliance, with the exception of the NOVASCREEN study.

Pharmacology

The primary pharmacodynamic *in vivo* and *in vitro* studies were directed at examining the anticonvulsive properties of ESL and its metabolites in well-known models for testing anticonvulsive activity (maximal electroshock, corneal kindling, different chemoconvulsant tests). The *in vitro* profile of ESL was established in a series of receptor binding studies and brain microdialysis studies. Analgesic activity of ESL was assessed in the mouse formalin paw test. Biological activity and selectivity was also evaluated *in vitro* (NOVASCREEN study).

- Primary pharmacodynamics

Primary pharmacodynamics was evaluated in many *in vitro* and *in vivo* studies.

Study results suggested that ESL did not interact with benzodiazepine, GABA and glutamate.

Pharmacological profile of ESL, assessed *in vivo* in mice and rats, suggested that eslicarbazepine acetate is an effective anticonvulsant and is able to protect against maximal electroshock seizure (MES) and a variety of convulsant agents. Further ESL may exert anticonvulsant properties by interfering selectively with rapidly firing neurones over neurones displaying normal activity.
Effects of ESL and its metabolites eslicarbazepine, R-licarbazepine and oxcarbazepine in the maximal electroconvulsive shock test were evaluated in male mice. Statistically significant decrease (-100%) in the number of tonic convulsion was observed after administration of 50 mg/kg and higher doses of all four test articles, for oxcarbazepine also after the 25 mg/kg dose. These studies revealed that, in mouse, eslicarbazepine is major metabolite of ESL and only a minor metabolite of (R)-licarbazepine and oxcarbazepine.

- Secondary pharmacodynamics

The Applicant presented only one secondary pharmacodynamic study investigating analgesic activity of ESL and its metabolites (eslicarbazepine, R-licarbazepine and oxcarbazepine) and indicated presence of analgesic activity for the test substances.

- Safety pharmacology programme

The safety pharmacology of ESL has been performed in mice, rats and dogs. In addition several *in vitro* studies were performed to assess cardiovascular risk.

Behavioural effects
No effects on gross behavioural or physiological state were observed in mice following oral treatment with ESL at the lower doses of 50 mg/kg. Dose-dependent sedative/myorelaxant effects (sedation, motor signs, decreased fear and reactivity to touch, abnormal gait) were observed with ESL over the dose-range from 250 to 500 mg/kg when given as a single oral gavage dose to male mice. Dose-dependent hypothermia was observed at 100, 250 and 500 mg/kg. Convulsions and Straub tail was observed at 500 mg/kg and mydriasis at 250 mg/kg. After a dose of 150 mg/kg or higher in rats almost identical symptoms occurred.

Renal function
ESL, at 50 or 100 mg/kg, had no effect on renal function (diuresis and urinary electrolyte excretion) in the mouse. At 250 mg/kg ESL significantly reduced urinary volume, sodium and potassium excretion and tended to decrease creatinine excretion. At 500 mg/kg, ESL markedly reduced or totally inhibited diuresis and markedly reduced sodium, potassium and creatinine excretion. Clinical signs of tremor, hypothermia, lack of motor coordination and marked sedation were also observed at 500 mg/kg. ESL,

at 15 or 50 mg/kg, had no effect on renal function in saline-loaded rats. At 150 mg/kg ESL may have had a small effect on renal function

Gastrointestinal transit
In mice both the gastrointestinal transit and gastric emptying was decreased at all doses tested. In rats 15 mg/kg had no effect on gastrointestinal function, higher doses inhibited gastrointestinal transit

Respiratory function
Respiratory function was assessed in conscious mice using whole body plethysmography. ESL reduced the transient changes in the respiratory parameters observed shortly after administration. Thereafter, 50 and 100 mg/kg p. o. of ESL had no significant effects on respiration up to the end of the four hour test period. After 200 mg/kg long-lasting effects suggestive of respiratory-depressant properties and an obstruction of the airway function was observed.

Cardiovascular system
Potential effects on the cardiovascular system have been investigated both *in vitro* and *in vivo* studies. No significant effect on arterial blood pressure, PR interval, QRS duration, QTc interval, left ventricular pressure variables, respiration rate, cardiac output, stroke volume, peripheral resistance, arterial blood gases, mean femoral arterial blood flow and conductance were shown.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted.

Pharmacokinetics

During the early phase of the development ESL and its metabolites were analysed by HPLC-MS and HPLC-UV methods, which did not distinguish between the enantiomeric monohydroxy metabolites (eslicarbazepine and R-licarbazepine). In the later phase, a chiral LC-MS/MS method was developed which allowed determination of eslicarbazepine and R-licarbazepine.
ESL is a prodrug which is hydrolysed to the main metabolite eslicarbazepine. Minor metabolites are OXC and R-licarbazepine. The metabolism of ESL is species-dependent. The metabolic profile of ESL in men is similar to the profile seen in mice, dogs and rabbits; whereas rat's metabolic profile is considerably different.

Toxicology

- Single dose toxicity

The single-dose toxicity of ESL was examined following oral or i.v. bolus administration to CD-1 mice or Sprague Dawley rats.

Summary of Single-Dose Toxicity

Species/ Strain	Doses (mg/kg)	Sex/Number/ Group	Approximate Lethal Dose (mg/kg)	Major findings	
Mouse/ CD-1	150, 300, 500 p.o.	5 ♂ + 5 ♀	500	-no mortality -subdued behaviour, abnormal gait, piloerection, closed eyes (M, F; HD) -1 F (HD) sacrificed for humane reasons	
Mouse/ CD-1	100 i.v. bolus	5 ♂ + 5 ♀	100	-mortality (1 F) -prostrate, breathing difficulties (M, F) -convulsions (F)	
Rat/ Sprague Dawley	150, 300, 500 p.o.	5 ♂ + 5 ♀	> 500	-no mortality -subdued behaviour, abnormal gait, piloerection, cold extremities (M, F; HD)) -↓body weight gain (M; HD)	
Rat/ Sprague Dawley	50, 100 i.v. bolus	5 ♂ + 5 ♀	< 50	-mortality (2 F, 2 M; LD)(2 F; HD) -3 F (HD), 5 M (HD) sacrificed for humane reasons	

Species/ Strain	Doses (mg/kg)	Sex/Number/ Group	Approximate Lethal Dose (mg/kg)	Major findings	
				-prostrate, breathing difficulties, dull eyes, salivation, red urine (M, F; LD, HD) -necropsy findings: reddened cervical lymph node (1 dead F; LD), reddened upper colon (1 dead M; LD), urinary bladder distended with red fluid (4 M, 3 F; HD), clear fluid in bladder (1 M; HD); speckled thymus (1 F; HD)	

F: female, M: male, LD: low dose, HD: high dose

The approximate lethal doses identified after oral application were 500 mg/kg in the mouse and more than 500 mg/kg in the rat. After bolus intravenous administration the approximate lethal doses were 100 mg/kg for the mouse and less than 50 mg/kg for the rat. Subdued behaviour, abnormal gait, piloerection, convulsions and breathing difficulties were signs immediately seen after drug application. These signs were no longer apparent on the day following dosing. Mortality was observed in mice and rats after intravenous application of ESL. Necropsy findings in rats were mainly related to the bladder.

Sedative / myorelaxant effects and bladder findings became apparent in the single-dose toxicity studies with ESL. The studies conducted are sufficient and no further single dose toxicity studies were required.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies with ESL were conducted in mouse, rat and dog. Additionally, studies with eslicarbazepine and R-licarbazpine were conducted in the rat. The rat was initially selected as rodent species, however, because the metabolic profile of ESL in mice was found to be much closer to that in human, additional studies were performed in mice.

Marked clinical signs (e.g. subdued behaviour, piloerection, unsteady gait) were observed in mice and/or dogs after ESL-treatment. Increases in liver weights including increases in cholesterol and centrilobular hypertrophy of the liver were observed after ESL-treatment of all animal species investigated.

These observations were attributed to liver enzyme induction. Liver enzyme induction has been demonstrated in mice following daily oral dosing for 5 days with ESL, OXC and CBZ at 30 mg/kg.

In the mouse, spleen findings (dose-related increase in weight and extramedullary hematopoiesis) were observed in male animals.
In the rat, clinical signs were not that obvious after ESL-treatment unlike that in mice and dogs. Increases in kidney weights and nephropathy, which were not completely reversible, were effects observed after ESL-treatment. Treatment of rats with the main human metabolite eslicarbazepine induced similar clinical signs like ESL-treatment of mice and dogs. Eslicarbazepine-treated rats showed also increased liver weights (with centrilobular hypertrophy of the liver and increases in cholesterol), lower thymus weights, epithelial hypertrophy of the thyroid and histopathological changes in the ovaries of female animals. R-licarbazepine treatment of rats was primarily associated with lesions in the liver and stomach of both sexes and in the kidneys of male animals.
In the dog, besides clinical signs and liver effects, extended aPTT values were the most obvious finding after ESL-treatment. aPTT changes probably reflect a reduction in liver synthetic capacity. Effects of ESL or eslicarbazepine treatment on reproductive organs were observed in rats and dogs, which were assessed under consideration of findings from the reproductive toxicity studies

Toxicokinetic studies were concurrently performed with all repeat-dose studies. ESL is rapidly metabolised in all animal species. The main metabolite observed in mice and dogs is eslicarbazepine followed by oxcarbazepine and only minor amounts of R-licarbazepine. In the rat, the main metabolite

is oxcarbazepine, followed by eslicarbazepine and minor amounts of R-licarbazepine. In humans, ESL is quickly metabolised to eslicarbazepine and only minor amounts of R-licarbazepine and oxcarbazepine. Therefore, the metabolite profile of ESL, respectively the systemic exposure towards the metabolites, in mice and dogs is much more similar to that in man than that in rats. However, if exposures towards eslicarbazepine, the main metabolite in humans, are compared, exposure ratios are appreciably lower in all animal species investigated. Therefore no safety margins can be calculated and this is reflected in the SPC (section 5.3).

- Genotoxicity

ESL was extensively tested in a battery of *in vitro* and *in vivo* tests for genotoxicity with AMES assay, mouse lymphoma test, chromosomal aberration in CHO and human peripheral lymphocytes, and *in vivo* mouse micronucleus test and mouse liver UDS test. From the results it can be concluded that ESL has some clastogenic activity in certain mammalian cell systems (mouse lymphoma and CHO cells) *in vitro* whereas in others (human peripheral lymphocytes) it obviously is negative. As ESL does not show any mutagenic activity in the AMES assay and *in vivo* assays in mouse with high exposures, the equivocal results in *in vitro* cytogenetic assays are not considered to be biologically relevant.

- Carcinogenicity

The rat metabolises ESL primarily to OXC, which represents approximately 86% of compound-derived circulating material. The relevance of conducting a carcinogenicity study in rats was thus questionable as, in effect, this would have had only very limited relevance to man, given that OXC circulates at only very low (≤1% of circulating material) levels in man following administration of ESL and the monohydroxy metabolites represent approximately 99% of circulating material. A study in rats was of no value and thus the mouse – in which the monohydroxy metabolites represent approximately 70-75% of circulating material (together with approximately 25% OXC) – becomes the species of choice for a carcinogenicity study. It therefore was considered valid to only investigate potential carcinogenicity in a single species, the mouse. This strategy had been discussed in scientific advice from both the Swedish Medical Products Agency and the FDA; both agencies agreed that a carcinogenicity study in rats would serve no purpose.

The 104 weeks mouse study showed clear evidence for ESL to be a potent rodent liver carcinogen which could have been expected given the relationship to oxcarbazepine and carbamazepine. Therapeutic relevance of the carcinogenic potential of ESL in rodents however is questionable due to the known sensitivity of mice to hepatic carcinogenicity when treated with inducers of hepatic enzymes and suggesting a species specific effect. Such effects are known from liver enzyme induction studies and carcinogenicity studies in rodents with the closely related substances oxcarbazepine and carbamazepine. Both also induced cell proliferation *in vitro* in CHO cells.
BIAL has substantiated its assumption that liver tumours found in mice have probably been caused by chronic induction of liver enzymes as demonstrated in the report AL081212. This report was filed retrospectively to summarize a study performed during drug development already in 2000. This study was not performed according to GLP requirements and this had been the reason for not submitting it with the original MAA. However the report shows that ESL significantly induced liver enzymatic activity of CYP2A6, CYP2C19, CYP2C9, CYP2E1 and CYP3A4 as indicated by higher transformation of the respective model substrates. Also the study seemed to be adequately performed and reliable. It therefore seems justified to assume hepatic effects observed in mice as being ultimately caused by the increase of liver metabolic function.

- Reproduction Toxicity

Like in repeat-dose studies, general toxic effects were observed in males and females treated with ESL in the reproductive toxicity studies. In a fertility study in male and female rats, impairment of female fertility by ESL was shown. In a fertility study in mice, developmental effects were observed in embryos; however, effects could also result from lower *corpora lutea* count and thus show impairment of fertility. *Corpora lutea* counts were determined but considered to be unreliable. No in-depth investigation was performed on male fertility in both fertility studies (e.g. no sperm analysis or epididymis weights missing). Embryotoxicity studies were performed in rats, mice and rabbits. Reduced foetal weights, minor skeletal abnormalities and variations as well as ossification delays were

observed in all embryotoxicity studies. In the mouse, the overall incidence of major abnormalities and the incidence for major skeletal abnormalities were increased. In the rat embryotoxicty study, statistically significant incomplete ossifications of various bones of the skull, thoracic vertebrae, sternum and pelvic girdle were observed. Concomitantly maternal toxicity was noticed, but no direct correlation could be drawn between maternal toxicity and toxic effects observed in foetuses. Studies on effects of ESL on the pre-postnatal development were performed in mice and rats. Trends towards prolonged gestation and increases in the duration of parturition were observed for ESL-treated rats. A delay in attainment of sexual development milestones of male and female pups was observed in both studies. In the rat study, pup mortality was observed which was related to poor maternal care. No effects on F_1 fertility parameters were observed in rats and mice. Milk transfer of eslicarbazepine was shown for mice. Altogether, exposure ratios of animal to human exposure to the main metabolite eslicarbazepine were low in the studies on reproductive toxicity. No safety margins exist.

- Toxicokinetic data

Concurrently with nearly all of the repeated dose studies, an evaluation of toxicokinetic parameters was performed. An achiral method was used for mouse and dog studies that did not differentiate between the two metabolites eslicarbazepine and R-licarbazepine. Accordingly, data about the formation of both isomers in mice and dogs have to be taken from other studies. Metabolite patterns obtained for mice and dogs after repeated dosing, show that ESL is quickly metabolised to BIA 2-005 (eslicarbazepine and R-licarbazepine) and oxcarbazepine. Systemic exposure towards BIA 2-005 is much higher in both species than to oxcarbazepine. For the mouse, a sex-related difference in the rate and/or routes of metabolism was observed. For the rat, data are available that differentiate between eslicarbazepine and R-licarbazepine. ESL was rapidly metabolised mainly to oxcarbazepine, followed by eslicarbazepine and to only minor amounts of R-licarbazepine. Sex-related differences in the amount of metabolites were observed that indicate a lower metabolising capacity in female rats.
Altogether, toxicokinetic parameters show that the metabolite profile of the mouse and dog is much more similar to humans than the rat. Therefore, repeated dose studies in mice and dogs with ESL are of more relevance for safety assessment.
According to the guideline on the evaluation of control samples in nonclinical safety studies, toxicokinetic data should have been presented from controls. However, most of the studies were performed before this guideline came into force, and is therefore acceptable.

- Local tolerance

No studies on local tolerance were performed, which is acceptable.

Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment which comprises the PECsw calculation according to the Guideline CHMP/SWP/4447/00-final. The $dose_{ai}$ used in this calculation is not correct and should be replaced by the expected maximum daily dose of 1200 mg. Under all other assumptions made by the applicant the higher dose leads to a PECsw of 11.73 ng/mL. Considering that a forecast of market success of a medicinal product cannot be taken into account in phase I of the ERA the PECsw will be 586.6 ng/mL. Because the action limit of 10 ng/ml is exceeded, a phase II assessment will be submitted as a follow-up measure.

2.4. Clinical aspects

Introduction

Exalief (ESL, Eslicarbazepine acetate, chemical name (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, BIA 2-093) was designed to constitute a third-generation, single-enantiomer member of the long-established family of first-line dibenz/b,f/azepine anti-epileptic drugs (AEDs) represented by carbamazepine (CBZ, first-generation) and oxcarbazepine (OXC, second-generation). Exalief shares with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide

substitute but is structurally different at the 10,11-position. This molecular variation results in differences in metabolism. Unlike CBZ, Exalief is not metabolised to CBZ-10,11-epoxide and is not susceptible to auto-induction of its own metabolism. Unlike OXC, which is metabolised to both Eslicarbazepine (also called S-licarbazepine or BIA 2-194) and R-licarbazepine (also called BIA 2-195), Exalief is a prodrug of Eslicarbazepine, which is the drug entity responsible for the ESL pharmacological effect.

Preclinical experiments suggest that both ESL and Eslicarbazepine competitively interact with site 2 of the inactivated state of a voltage-gated sodium channel (VGSC), preventing its return to the active state and repetitive neuronal firing.
The precise mechanism by which ESL exerts its antiepileptic effects remains to be fully elucidated.
ESL was tested in several animal seizure models predictive of anticonvulsant efficacy, such as the maximal electroshock seizure test in rats and mice and the corneal kindling in mice. ESL also showed protective effects against seizures induced by several chemoconvulsants in rats or mice, namely metrazole, bicuculline, picrotoxin, and 4-aminopyridine (4-AP).

BIAL submitted an application for Exalief tablets in the proposed target indication of adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. The recommended maintenance dose of Exalief is 800 mg once daily which may be increased to 1200 mg once daily.

Exalief has been developed as tablets of 400 mg, 600 mg and 800 mg. In addition, during the clinical development, a solution has been used.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

Pharmacokinetics

Introduction

The pharmacokinetics of Exalief and its metabolites have been investigated in 24 clinical studies.

Absorption

- Bioavailability

Eslicarbazepine acetate (BIA 2-093) is a prodrug of eslicarbazepine. Following oral administration, plasma levels of eslicarbazepine acetate usually remain below the limit of quantification. Eslicarbazepine t_{max} is attained at 2-3 hours (h) post-dose. Bioavailability is considered high since the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose and the main metabolite eslicarbazepine was responsible for more than 95% of systemic exposure after administration of eslicarbazepine acetate.

1. Study No. BIA-2093-104

Study No. BIA-2093-104 was a single centre, open label, randomized, two-way crossover study. In 12 healthy male and female volunteers the tolerability and pharmacokinetics of eslicarbazepine acetate vs. oxcarbazepine and their metabolites were investigated. A single 900 mg oral dose of eslicarbazepine acetate respectively oxcarbazepine was administered.

Serum drug levels were monitored for 96 hours following dosing, which was sufficient to meet the 80% rule for determination of AUC_{inf} for Eslicarbazepine and oxcarbazepine. According to the study report Eslicarbazepine acetate could not be determined as the plasma concentration was systemically found to be below the limit of quantification.
A dosage strength not intended for marketing was used as investigational product and the composition of the drug product is not stated. Therefore this study is only supportive.

Following a single oral dose of 900 mg, eslicarbazepine acetate appeared to be rapidly and extensively metabolised to Eslicarbazepine.

The ratio of AUC_t and AUC_∞ is <80% for oxcarbazepine after administration of Exalief. However, its C_{max} and AUC levels are found to be below 1% (calculated to Eslicarbazepine). It is therefore agreed that this substance is not a main metabolite.

After a single dose of Exalief the t_{max} of R-licarbazepine occurs later and C_{max} and AUC levels are lower compared to after administration of the oxcarbazepine product. These results are to be expected, as two additional metabolic steps are necessary in the formation of R-licarbazepine from eslicarbazepine acetate i.e.eslicarbazepine acetate→ eslicarbazepine → Oxcarbazepine→ R-licarbazepine.

2. Study No. BIA-2093-110

Study No. BIA-2093-110 is a single centre, open label, randomized, multiple-dose three-way crossover study. In 12 healthy male and female volunteers the tolerability and pharmacokinetics of eslicarbazepine acetate vs. Oxcarbazepine and their metabolites were investigated.

Serum drug levels were followed for day 1 to day 7 for pre-morning dose and for 96 hours following dosing on day 8.
According to the study report Eslicarbazepine acetate could not be determined as the systemic plasma concentration was found below the limit of quantification.
The sampling schedule was appropriate for accurate determination of $C_{max\ ss}$. The washout period of 10 -15 days between phases was sufficient to ensure unquantifiable plasma levels at the start of consecutive period (except subject #1).

The randomisation schemes were balanced for sequence and appear random.

A dosage strength not intended for marketing was used as investigational product and the composition of drug product is not stated. Therefore this is has only supportive.

Pharmacokinetic Results

Treatment (geometric mean)	C_{max} (Eslicarbazepine) (ng/mL)	C_{min} (Eslicarbazepine) (ng/mL)	Fluctuation (%)	$AUC_{0-\tau}$ (sum all metabolites) (ng.h/mL)	C_{max} (sum all metabolites) (ng.h/mL)
eslicarbazepine acetate 1x900 mg/day	21103	6980	127	304609	24966 ng/mL
eslicarbazepine acetate 2x450 mg/day	16233	9207	66.7	148935	17089 ng/mL
OXC 2x450 mg/day	12055	8650	38.4	149875	15490 ng/mL

The proportion ratios of the metabolites found appear congruent with the results of the precursor eslicarbazepine.

Cumulative C_{max} of the sum of eslicarbazepine + R-licarbazepine + oxcarbazepine was 29% higher following administration of eslicarbazepine acetate 900 mg once-daily in comparison with BIA eslicarbazepine acetate 450 mg twice-daily. The ratio of geometric means of AUC during 24 hours between once daily/twice daily regimen was about 1.
C_{min} of eslicarbazepine acetate under once daily regimen is decreased and the fluctuation is increased almost twofold in comparison to twice daily administration.

Cumulative plasma C_{max} of eslicarbazepine + R-licarbazepine + oxcarbazepine was 10% higher following administration of eslicarbazepine acetate 450 mg twice-daily in comparison with OXC 450 mg twice daily. The ratio of geometric means of cumulative AUC during 24 hours between once eslicarbazepine acetate and OXC regimen was about 1.

Based on pharmacokinetical data an once a day regimen could be of disadvantage, as the fluctuation is more pronounced. Steady state (eslicarbazepine acetate) seems to be achieved after 4-5 days in any regimen.

3. Study No. BIA-2093-115

Study No. BIA-2093-115 was a single centre, open label, randomized, two period, four group parallel design study. 8 healthy adult volunteers were randomised per group. No dropouts were reported.
In each group, the study consisted of a single-dose period (Phase A) followed by a multiple dose period of 7 days duration in which the investigational product was administered once daily (Phase B).

Serum drug levels were followed for 96 hours in Phase A and in Phase B on day 6 and 10 at pre-dose and on day 11 for 96 hours.
According to the study report Eslicarbazepine acetate could not be determined as the plasma concentration was systemically found below the limit of quantification.
The sampling schedule was appropriate for accurate determination of C_{max}. The duration of the multiple period was considered sufficient to reach steady state levels.

Statistical methods and Variables

No statistical analysis has been performed.
Parameters investigated: Cmax, tmax, Cmin, AUC0-t AUC0-τ AUC0-∞ λz, degree of accumulation

Pharmacokinetic Results

The proportion ratios of the metabolites found appear to be congruent with the results of the other PK studies.

Eslicarbazepine was the major circulating drug entity except for group 4 (450 mg R-licarbazepine) where it reached 11% and 18% levels if compared to R-licarbazepine.
Oxcarbazepine was a minor metabolite in any group.
The results indicate that eslicarbazepine has a better bioavailability than its R-enantiomer, following oral administration.
Steady state for eslicarbazepine under Exalief therapy seems to be achieved after 4-5 days.

- Bioequivalence

Two bioequivalence studies have been performed. In the first one (BIA-2093-109), a tablet formulation has been compared to an oral suspension. As “oral suspension” is not part of this application, the assessment is focused on the tablets. In the second study (BIA-2093-122) the bioequivalence between the clinical trial formulation and the formulation to be marketed has been investigated.

Pharmacokinetic Results

The 90% confidence interval (CI) of all parameters under consideration (BIA 2-005 Cmax, AUC0-t, and AUC0-∞) were within the acceptance range of [80%; 125%]. Therefore, the TBM formulation and the formulation used in the pivotal clinical trials were considered bioequivalent.

The results showed no statistical difference for extent and rate of formation of the main metabolite. Therefore the hypothesis of bioequivalence can be accepted. The formulations can be considered as interchangeable.
Adverse events were reported both for the test and the reference product. No death or other serious adverse events were reported.
The results do not indicate that the adverse events are dose related.

- Influence of food

Two studies have been performed to investigate the food effect on orally administered eslicarbazepine acetate. Both studies showed that food has no relevant effect on eslicarbazepine acetate pharmacokinetics.

Distribution

The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent of concentration. In vitro studies have shown that the plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, PHT and tolbutamide. The binding of warfarin, diazepam, digoxin, PHT and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Elimination

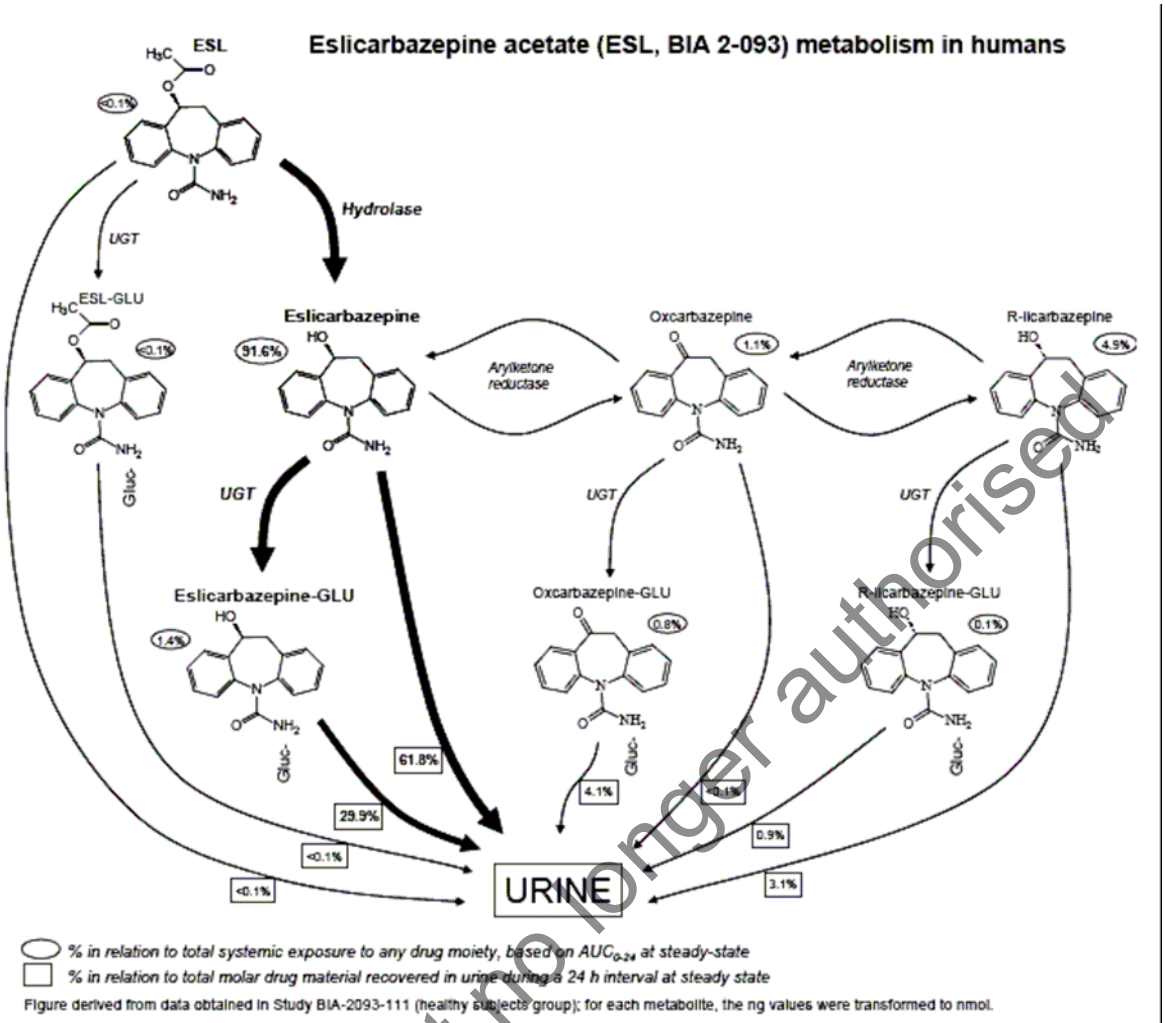
- Excretion

Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, Eslicarbazepine and its glucuronide correspond to more than 90% of total drug material excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.
The rate and excretion has been sufficiently characterised during the renal impairment study (BIA-2093-112). For a detailed assessment of this study please see the section “Special populations”.

- Metabolism

Eslicarbazepine acetate is rapidly and extensively biotransformed to eslicarbazepine by hydrolytic first-pass metabolism. In studies in healthy subjects and epileptic adults, the apparent half-life of Eslicarbazepine was 10- 20 h and 13-20 h, respectively. Peak plasma concentrations (Cmax) of eslicarbazepine are attained at 2-3 h post-dose and steady state of plasma concentrations is attained after 4-5 days of QD dosing, consistent with an effective half-life in the order of 20-24 h. Minor metabolites in plasma are R-licarbazepine and OXC, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and OXC.

The metabolism of BIA 2-93 has been sufficiently characterised. The proportions of the metabolites were consistent within all studies (BIA-2093-104/110/115). For a detailed assessment of the studies please see the section “Absorption”.



- Inter-conversion

Interconversion of the S- to the R-enantiomer is minor pathway of the biotransformation process, as described in the section above.

- Consequences of possible genetic polymorphism

No studies on genetic polymorphism have been provided. The majority of subjects were non-black healthy adults.

Dose proportionality and time dependency

- Dose proportionality

The dose proportionality of eslicarbazepine acetate in adult patients has been investigated in a sub-study of one of the pivotal trials.

1. STUDY NO. BIA-2093-301 PK SUB-STUDY

This study was performed in a subset of patients who had already completed a 1-year open-label extension (Part II) of clinical study BIA-2093-301, and who were entering an additional 1-year open-label extension (Part III) of this study. Blood samples for PK assessment were taken in a subset of 51 patients during one of the regular clinical visits.

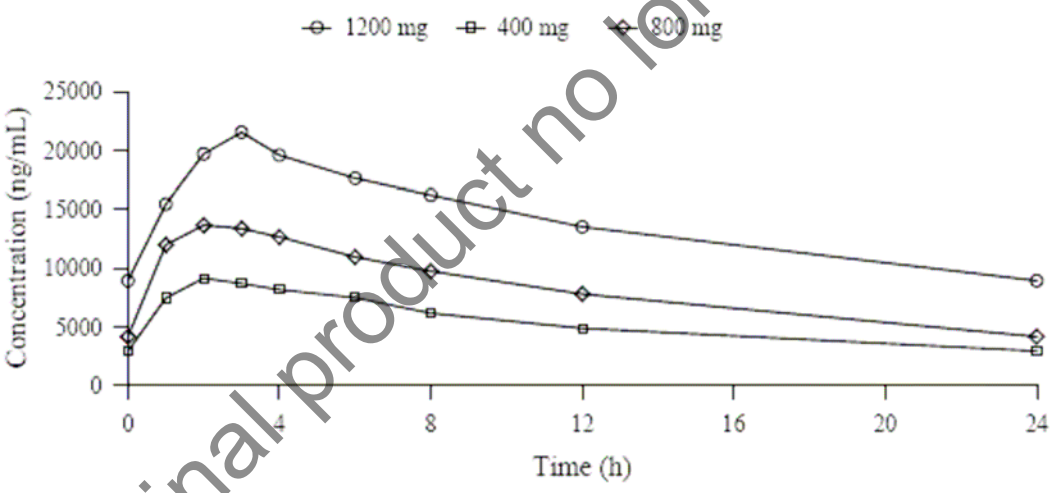
51 male and female patients were evaluated. The patients are distributed in three dosage groups

Daily intake	n =
400 mg eslicarbazepine acetate	7
800 mg eslicarbazepine acetate	26
1200 mg eslicarbazepine acetate	18

Blood samples for PK evaluation were taken at the following time-points in relation to dosing: pre-dose, and 1, 2, 3, 4, 6, 8, and 12 hours post-dose.
Serum drug levels were analysed for (1, 2, 3, 4, 6, 8, 12) 24 hours following dosing for eslicarbazepine acetate and its metabolites eslicarbazepine, R-licarbazepine and OXC. According to the study report Eslicarbazepine acetate could not be determined as the plasma concentration was systemically found to be below limit of quantification. The reduced sampling schedule was considered inappropriate for accurate determination of C_{max} , but the Applicant clarified that to apply a reduced sampling schedule in patient studies compared to healthy subject studies is reasonable both from an ethical and practical point of view, provided that the sampling times chosen are appropriate for determination of the full PK profile.
This was considered acceptable.

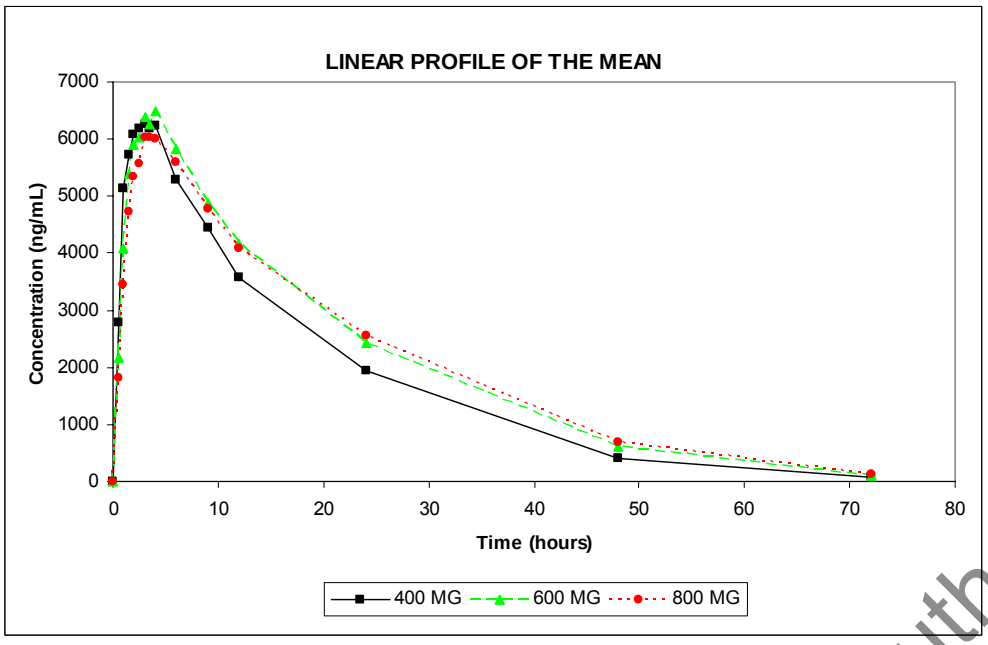
Mean plasma concentration time profiles of eslicarbazepine following once daily (QD) dosing with 400 mg, 800 mg or 1200 mg of Exalief in study [BIA-2093-301] are presented in Figure A.

Figure A. Mean eslicarbazepine (BIA 2-194) plasma concentration-time profiles following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



Following oral administration of Exalief 400 mg, 800 mg, and 1200 mg, Eslicarbazepine t_{max} was reached between 1 and 6 h post-dose (median of 2.0 h), 2 and 6 h post-dose (median of 2.0 h), and 1 and 6 h post-dose (median of 2.5 h), respectively. Thereafter, plasma Eslicarbazepine concentrations declined in a multiphasic manner with an apparent t1/2 of 12.8 h, 13.5 h, and 20.2 h, following oral administration of Exalief 400 mg, 800 mg, and 1200 mg, respectively. Systemic exposure to Eslicarbazepine appears to be dose-proportional following oral administration of Exalief 400 mg, 800 mg and 1200 mg.

The dose proportionality could not be concluded by these initially presented results. The CHMP requested that the dose proportionality be visually evaluated, too, and recommended to show that the dose normalised curves were super imposable. The Applicant replied in the day 120 responses providing the requested mean plasma concentration time profiles after dose normalisation to a 400 mg dose following single doses of the 400 mg, 600 mg and 800 mg tablets of the commercial formulation.



Although conventional limits as postulated for a regular bioequivalence approach are not always met, the linear pharmacokinetics can be concluded in the context of overall data and visual evaluation of the dose normalised plasma curves.
In conclusion, based on the [BIA-2093-301 PK Sub-Study] results and taking into account information from other clinical trials, it seems reasonable to conclude that the PK of eslicarbazepine can be regarded as dose-proportional.

- Time dependency

There was no time dependency of the Eslicarbazepine PK.

Intra- and inter-individual variability

Interindividual variability in the extent of systemic exposure to the main metabolite BIA 2-005 was relatively low through all studies. Intra-subject variability of AUC and Cmax was lower than 15%.

Pharmacokinetics in target population

The findings about the rate and the extent of absorption and metabolism of Exalief are in line with the PK study in healthy adults (BIA-2093-301).

Special populations

- Impaired renal function

Exalief and its metabolites are mainly renally excreted. Significant increases in the extent of systemic exposure to its metabolites were found in study BIA-2093-112, the magnitude of which depended on the degree of renal impairment. These findings all point to a reduced ability of kidneys with impaired function to excrete Exalief or its metabolites. Therefore, dose adjustment is required in patients with impaired renal function and is reflected in the SPC.
The main metabolites were effectively removed by repeated dialysis from the circulation of patients with end-stage renal disease.

STUDY NO. BIA-2093-112

Study design

Study No. BIA-2093-112 an open-label, single-dose, single-centre, parallel group study in 5 groups of subjects with different degrees of renal function:
Group 1 – normal renal function (creatinine clearance > 80 mL/min)
Group 2 – mild renal impairment (creatinine clearance 50-80 mL/min)
Group 3 – moderate renal impairment (creatinine clearance 30-50 mL/min)
Group 4 – severe renal impairment (creatinine clearance <30 mL/min)
Group 5 – end stage renal disease, requiring haemodialysis (ESRD)

Safety evaluation was performed before starting groups 3 and 4 and before starting group 5.
Objective as to characterise the pharmacokinetics (PK) of Exalief and its metabolites eslicarbazepine, R-licarbazepine, oxcarbazepine, BIA 2-093 glucuronide, BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide in subjects with renal impairment.
During the whole study, subjects received a single dose of 800 mg Exalief.

Serum drug levels were followed for 96 hours and urine levels for 72 h following dosing.
The sampling schedule was appropriate for accurate determination of C_{max}.
Subjects in the ESRD group were dialyzed at 12 hours post-medication.

Population studied

8 subjects were enrolled in the control group and each renal impairment group. Overall 40 patients were enrolled all of which completed the study. The functional groups are based on creatinine clearance measured by the Cockcroft-Gault Equation.

Statistical methods and pharmacokinetic Variables

The following parameters were calculated:
$C_{max,}$ $AUC_{0\text{-}Inf}$, $AUC_{0\text{-}t\ last}$, t_{max}, $t_{1/2.}$ $Clearance_{(apparent/renal),}$ volume of distribution.
ANOVA for the above stated parameters (except for $t_{max),}$ 95% CIs are calculated.

Pharmacokinetic Results

Concentrations of Exalief and its glucuronide in plasma and urine were below LLOQ for most of the subjects. The quantifiable concentrations amounts were found at a very low level. Therefore the mother compound is considered negligible.

The metabolites R-licarbazepine and OXC showed quantifiable plasma levels. Results for the pharmacokinetic variables and statistical analysis are provided in the clinical study report. The relative proportion of active moieties remained reasonably similar in the different groups.
For clarity reasons detailed data of these metabolites were omitted.

Statistical Analysis for BIA 2-194 in human Plasma

Variable (unit)	Normal renal function group (n = 8)	Mild renal impairment group (n = 8)	%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group (n = 8)	%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group (n = 8)	%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	LSMean	LSMean			LSMean			LSMean		
C_{max} (ng/mL)	14286.790	18677.265	130.73	(105.63 ; 161.80)	15055.632	105.38	(85.15 ; 130.42)	149 74.791	104.82	(84.69 ; 129.72)
AUC(0-12h) (hr·ng/mL)	105275.733	150945.034	143.38	(118.20 ; 173.93)	138473.115	131.53	(108.43 ; 159.56)	138262.814	131.33	(108.27 ; 159.31)
AUC(0-t_{last}) (hr·ng/mL)	234378.938	378771.695	161.61	(130.82 ; 199.64)	483013.562	206.08	(166.82 ; 254.58)	540596.674	230.65	(186.71 ; 284.93)
AUC(0-∞) (hr·ng/mL)	236833.693	381572.116	161.11	(118.02 ; 219.95)	500036.696	211.13	(154.65 ; 288.24)	600502.701	253.55	(185.73 ; 346.15)
$t_{½,z}$ (hr)	10.711	10.605	99.02	(71.66 ; 136.82)	17.853	166.69	(120.63 ; 230.32)	28.306	264.28	(191.27 ; 365.18)
CL/F (l/hr)	3.378	2.097	62.06	(45.46 ; 84.73)	1.600	47.37	(34.70 ; 64.66)	1.332	39.44	(28.89 ; 53.84)
V_z/F (L)	52.195	32.078	61.46	(50.16 ; 75.31)	41.207	78.95	(64.43 ; 96.74)	54.403	104.23	(85.06 ; 127.72)
CL_R *(mL/h)*	1035.146	614.355	59.35	(41.93 ; 84.02)	221.49	21.36	(15.09 ; 30.24)	93.371	9.02	(6.37 ; 12.77)
T_{max} (hr)*	1.000	1.000	p-value: 0.4987		2.875	p-value: 0.0198		2.875	p-value: 0.0315	

* Medians, p-value according to Wilcoxon signed rank test
Data Source: Section 14.1, Tables 117, 118, 119, 173, 174, 175, 349, 350 and 351

Variable	Normal renal function group (n = 8)	ESRD (n = 8)	%Ratio (Impaired/Control	95% Confidence Interval of ratio
	LSMean	LSMean		
C_{max} (ng/mL)	14286.790	14510.197	101.56	(82.06 ; 125.70)
AUC(0-12h) (hr·ng/mL)	105275.733	134757.936	128.00	(105.52 ; 155.27)
AUC(0-t_{last})	234378.938	134757.936	57.50	(46.54 ; 71.03)
AUC(0-∞) (hr·ng/mL)	236833.693	333137.783	140.66	(103.04 ; 192.03)
$t_{½,z}$ (hr)	10.711	14.339	133.88	(96.89 ; 184.99)
Cl/F (l/hr)	3.378	2.402	71.09	(52.08 ; 97.06)
V_z/F (L)	52.195	49.677	95.18	(77.67 ; 116.62)
CL_R *(mL/h)*	1035.146	22.753	2.20	(1.44 ; 3.36)
T_{max} (hr) *	1.000	1.500	p-value: 0.1626	

* Medians, p-value according to Wilcoxon signed rank test
Data Source: Section 14.1, Tables 120, 176 and 352

Pharmacokinetic variables of glucuronidated metabolites

C_{max}	Group 1 (control)	Group 2 (mild)		Group 3 (moderate)		Group 4 (severe)		Group 5 (ESRD)	
	ng/ml	ng/ml	% ratio	ng/ml	% ratio	ng/ml	% ratio	ng/ml	% ratio
BIA2-194 Gluc.	1859	965	**51**	3345	**180**	3307	**177**	5492	**295**
BIA2-195-Gluc.	45	70	**155**	128	**282**	241	**531**	103	229
OXC-Gluc.	73	127	**173**	274	**374**	617	**841**	-	-

$AUC_{0-\infty}$	Group 1 (control)	Group 2 (mild)	Group 3 (moderate)	Group 4 (severe)	Group 5 (ESRD)

	h* ng/ml	h* ng/ml	% ratio	h* ng/ml	% ratio	h* ng/ml	% ratio	h* ng/ml	% ratio
BIA2-194 Gluc.	32721	43425	**133**	191192	**584**	379148	**1158**	70803	**216**
BIA2-195-Gluc.	652	4076	**625**	13440	**2061**	67493	**10351**	212	**33**
OXC-Gluc.	1781	6045	**339**	18699	**1049**	47844	**2686**	-	-

CL_R	Group 1 (control)	Group 2 (mild)		Group 3 (moderate)		Group 4 (severe)		Group 5 (ESRD)	
	mL/h	mL/h	% ratio	mL/h	% ratio	mL/h	% ratio	mL/h	% ratio
BIA2-194 Gluc.	5978	5060	**85**	1215	**20**	471	**8**	222	**3**
BIA2-195-Gluc.	11818	2127	**18**	648	**5**	111	**1**	204	**2**
OXC-Gluc.	7238	2810	**38**	1033	**14**	351	**5**	-	-

Results of the control group were consistent with findings in the other studies of this application.

Results concerning the phase I metabolites eslicarbazepine (about 95% of the drug exposure), R-licarbazepine and OXC were as expected (for mainly renal eliminated substances): C_{max} remained generally unaffected. Concerning AUC, a clear tendency to increase and for the t_{max} to decrease was seen. The effect increased with increasing degrees of renal impairment. Clearance (renal and apparent) decreased with increased renal impairment.
Apparent terminal elimination half-life was increased in the moderate and severe renal impairment groups.

The glucuronated metabolites were affected in a disproportionally stronger manner:
For the AUC no clear linear relationship was observed, but values for the moderate and severe renal impairment groups were much higher than for the normal and mild groups and the clearance decreased strongly with higher degree of renal impairment.

In the ESRD group mean plasma concentrations of metabolites were effectively reduced by dialysis. However, it was only after the second dialysis that plasma concentrations were reduced to low levels approaching LLOQ (lower limit of quantitation). In the case of BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide plasma concentrations increased markedly after the first dialysis.

- Impaired hepatic function

The pharmacokinetics of Exalief in patients with mild to moderate hepatic impairment showed that inhibition of the hepatic metabolism of the parent drug affected the formation of its main metabolite eslicarbazepine. However this finding is considered not to be of clinical relevance. Therefore the results of study (BIA-2093-111) do not indicate the necessity of a dose adjustment in patients with mild to moderate hepatic impairment.

STUDY NO. BIA-2093-111

Study design
Study No. BIA-2093-111 an open-label, multiple-dose, single-centre, parallel group study in 2 groups of subjects: subjects with moderate hepatic impairment and healthy controls. The study is divided in a single dose phase (day 1) and steady state phase (sampling on day 8).

Objective: To characterise the pharmacokinetics (PK) of Exalief and its metabolites (eslicarbazepine, R-licarbazepine, oxcarbazepine, BIA 2-093 glucuronide, BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide) in subjects with moderate hepatic impairment.

During the whole study, subjects received a dose of 800 mg Exalief once daily over 8 days .
Serum drug levels were followed for 24 hours and urine levels for 96 h following dosing.
The sampling schedule was appropriate for accurate determination of C_{max}.

Test product
Tablets containing 800 mg of eslicarbazepine acetate provided by BIAL.

Population studied
Nine subjects were enrolled in the hepatic impairment group [with a Child-Pugh category of moderate impairment (a Child-Pugh score of 7 to 9)], of which 8 completed the study, and 8 subjects were enrolled in the healthy control group, of which all completed the study.

Bioanalytics
The amount of conjugated metabolites is investigated indirectly: After treatment with β-glucoronidase the samples will reanalysed. The difference of the two measurements reflects the amount of conjugated metabolites.

Statistical methods and pharmacokinetic Variables
The following parameter were calculated for the single dose phase: $C_{max,}$ AUC $_{0\text{-Inf}}$, AUC $_{0\text{-t last}}$, t_{max}, $t_{1/2.}$
Parameters in the steady state: AUC_{ss}, $C_{max\ ss}$, C_{min}, $T_{max\ ss}$, $t_{1/2,}$ Clearance ($_{apparent/renal),}$ volume of distribution.
ANOVA for the above stated parameters (except for $t_{max),}$ the 95% CI are calculated.

Pharmacokinetical Results
BIA 2-093 glucuronide findings were below LLOQ in most of the subjects and BIA 2-195 concentrations are considered negligible
The plasma levels of eslicarbazepine acetate in subjects with hepatic impairment showed higher concentrations than in the control groups. The inhibition of the hepatic metabolism of the parent drug is therefore considered evident. However, the concentration of eslicarbazepine acetate in plasma was still very low (0.01%) in comparison with those observed for the main metabolite BIA 2-194.
Furthermore, no significant difference was found between the hepatic impaired group and the healthy control group for BIA 2-194 and its glucuronide in plasma.
Therefore the clinical finding is considered to have no clinical relevance.
The SPC will therefore state that no dose adjustment is needed in patients with mild to moderate hepatic impairment. The pharmacokinetics of eslicarbazepine has not been evaluated in patients with severe hepatic impairment and use in these patients is therefore not recommended.

- Gender

The results of a study (BIA-2093-105- see under "Elderly" below) do not indicate that gender has an impact on pharmacokinetic parameters.

- Race

No information on pharmacokinetic in different races or genetic polymorphism were provided.

- Weight

The effect of BMI on the pharmacokinetics has not been studied. This is acceptable as the drug substance is individually titrated.

- Elderly

STUDY NO. BIA-2093-105

Study design
Study No. BIA-2093-105 was a single centre, open label, non-randomized, parallel group study. The study consisted of a single-dose phase (Phase A) followed by a multiple-dose phase (Phase B). Phase B started 96 hours after Phase A dosing.
During the whole study, subjects received a single 600 mg dose of Exalief (Phase A) followed by 600 mg Exalief once daily for 8 days in Phase B.
Serum drug levels were followed for 72 hours following dosing, which was sufficient to meet the 80% rule for determination of AUC_{inf} for BIA 2-005. According to the study report Eslicarbazepine acetate could not be determined as the plasma concentration was systemically found to be below limit of quantification.
The sampling schedule was appropriate for accurate determination of C_{max}. There was no washout period between the two phases.

Test and reference products
Tablets containing 600 mg of eslicarbazepine acetate.

Population studied
30 subjects [14 healthy elderly (7 male and 7 female) and 16 healthy young (8 male and 8 female) were analysed. One dropout in the young group is reported (discontinued before receiving any dose).

Pharmacokinetic Results
For clarity reasons only results for BIA 2-194 (Eslicarbazepine) are presented and discussed in this report, because it is the main metabolite (about 90%) of Exalief.

Eslicarbazepine - Point estimates and 90% confidence intervals for the comparison of pharmacokinetic parameters evaluated for Test (elderly) and Reference (young)

Age effect (single-dose)		Test/Reference
C_{max}	PE	0.95
(ng/mL)	90% CI	0.82;1.09
$AUC_{0-\tau}$	PE	1.02
(ng.h/mL)	90% CI	0.87;1.18
$AUC_{0-\infty}$	PE	1.06
(ng.h/mL)	90% CI	0.89;1.26

PE = Point Estimate; CI = Confidence Interval.
The post-hoc power values for C_{max}, $AUC_{0-\tau}$ and $AUC_{0-\infty}$ are 83.5%, 79.6% and 67.4%, respectively.

Eslicarbazepine -Point estimates and 90% confidence intervals for the comparison of pharmacokinetic parameters evaluated for Test (elderly) and Reference (young)

Age effect (multiple-dose)		Test/Reference
Cmax	PE	0.88
(ng/mL)	90% CI	0.78;0.99
AUC0-τ	PE	0.98
(ng.h/mL)	90% CI	0.87;1.11
AUC0-∞	PE	1.01
(ng.h/mL)	90% CI	0.88;1.16

PE = Point Estimate; CI = Confidence Interval.
The post-hoc power values for Cmax, AUC0-τ and AUC0-∞ are 92.2%, 92.1% and 85.1%, respectively.

Point estimates and 90% confidence intervals for the comparison of pharmacokinetic parameters evaluated for Test (female) and Reference (male)

Gender effect (single-dose)		Test/Reference
C_{max}	PE	1.09
(ng/mL)	90% CI	0.94;1.25
$AUC_{0-\tau}$	PE	1.16
(ng.h/mL)	90% CI	1.01;1.33
$AUC_{0-\infty}$	PE	1.17
(ng.h/mL)	90% CI	0.99;1.38

PE = Point Estimate; CI = Confidence Interval.
The post-hoc power values for Cmax, AUC0-τ and AUC0-∞ are 84.3%, 84.1% and 71.0%, respectively.

Point estimates and 90% confidence Intervals for the comparison of pharmacokinetic parameters evaluated for Test (female) and Reference (male)

Gender Effect (Multiple-dose)		Test/Reference
C_{max}	PE	1.10
(ng/mL)	90% CI	0.97;1.25
$AUC_{0-\tau}$	PE	1.04
(ng.h/mL)	90% CI	0.92;1.17
$AUC_{0-\infty}$	PE	1.01
(ng.h/mL)	90% CI	0.88;1.16

PE = Point Estimate; CI = Confidence Interval.
The post-hoc power values for C_{max}, $AUC_{0-\tau}$ and $AUC_{0-\infty}$ are 90.8%, 92.4% and 85.1%, respectively.

For age and gender effects, 90% CI for all metrics includes the unit which means that there are no significant statistical differences associated with age or gender for the main PK parameters of Exalief, except for the parameter $AUC_{0-\tau}$ after single dose (gender). However the CI misses the unit shortly and the observation is not confirmed under multiple dose treatment. For a majority of the metrics the 90% CI were even within the acceptance range for bioequivalence (80-125%). Therefore, it can be concluded that the results clearly support the absence of clinically relevant differences between elderly and young subjects as well as between female and male subjects.

- Children

It should be noted that the treatment of children is not part of the application and that a PIP will be submitted after marketing authorisation has been granted.

STUDY NO. BIA-2093-202

Study design

Study No. BIA-2093-202 is an open-label, single-centre, multiple-dose study, in 30 paediatric epileptic patients distributed by 3 age groups of 10 patients each: 2-6 years [Group 1], 7-11 years [Group 2], and 12-17 years [Group 3].

The study consisted of 3 consecutive 4-week treatment periods in which patients received Exalief once-daily 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 less (weeks 9–12). At the end of each 4-weeks treatment period, patients were hospitalised and serial blood samples for drug assays were obtained over a dosing interval.

The objective was the characterisation of the pharmacokinetics of Eslicarbazepine acetate in children and adolescents with epilepsy.

Serum drug levels were followed for 12 hours following dosing for Exalief and its main metabolites eslicarbazepine, R-licarbazepine and OXC. According to the study report Eslicarbazepine acetate could not be determined as the plasma concentration was systemically found to be below limit of quantification.
The reduced sampling schedule is considered still appropriate for accurate determination of C_{max}. The periods were not separated by a washout phase.

Concomitant medication
Doses of 1 to 3 concomitant anti epileptic drugs (other than OXC and carbamazepine) were kept stable from 1 month prior to enrolment into the baseline phase and throughout the study, unless clinically unacceptable. Intermittent use of benzodiazepines was allowed.

Test products
The investigational products consisted of Eslicarbazepine acetate tablets in strengths of 200 mg, 400 mg, 600 mg and 800 mg and an oral suspension of 50 mg/mL.
Bioequivalence of the suspension, which is not part of the application, with the solid dosage form has been previously demonstrated.

Population studied
31 male and female patients with a documented diagnosis of partial-onset seizures at the age of 2-17 years (group 1 n=12; group 2 n= 8; group 3 n=11) were enrolled. 26 completed all treatment periods.

Statistical methods and pharmacokinetic Variables
No statistical analysis for pharmacokinetic parameters.
Parameters determined are: C_{max}, t_{max}, $AUC_{t\ last}$, $AUC_{0\text{-}Inf}$, $t_{1/2}$ and clearance.

PK results :PK parameters for BIA 2-194

Dose/ Age Group	C_{max} ng/mL	t_{max} h	AUC_{last} ng.h/mL	$AUC_{0-\infty}$ ng.h/mL	AUC_{τ} ng.h/mL	$t_{1/2}$ h	CLss/F mL/h/kg
Dosage regimen 5 mg/kg/day							
Group 1 (n=11) (2-6 yrs)	6921 (1794)	1 (1)	53599 (14351)	57073 (16654)	53599 (14351)	6 (1)	100 (29)
Group 2 (n=8) (7-11 yrs)	4820 (1693)	2 (1)	51748 (21492)	61012 (30846)	51748 (21492)	8 (2)	112 (47)
Group 3 (n=10) (12-17 yrs)	6382 (1854)	2 (1)	83691 (20997)	108436 (31143)	83691 (20997)	11 (2)	63 (16)
Dosage regimen 15 mg/kg/day							
Group 1 (n=10) (2-6 yrs)	16183 (3609)	2 (1)	169925 (42671)	198089 (62876)	169925 (42671)	8 (2)	94 (24)
Group 2 (n=8) (7-11 yrs)	16395 (3680)	3 (1)	206080 (39829)	256646 (55796)	206080 (39829)	10 (2)	76 (17)
Group 3 (n=10) (12-17 yrs)	17194 (3410)	2 (1)	251638 (54972)	374430 (116140)	251638 (54972)	14 (4)	63 (15)
Dosage regimen 30 mg/kg/day							
Group 1 (n=9) (2-6 yrs)	29935 (4627)	1 (0)	339387 (76600)	431533 (130594)	339387 (76600)	10 (3)	94 (28)
Group 2 (n=7) (7-11 yrs)	26890 (6944)	3 (1)	378259 (85989)	507645 (117245)	378259 (85989)	12 (4)	84 (25)
Group 3 (n=8) (12-17 yrs)	32400 (6005)	3 (2)	476183 (70624)	730724 (156745)	476183 (70624)	15 (4)	64 (10)

Eslicarbazepine acetate showed dose-proportional pharmacokinetics in epileptic children of different age groups treated with Eslicarbazepine acetate concomitantly with anti-epileptic drugs. Similarly to what occurs in adult subjects, Eslicarbazepine acetate was rapidly metabolised to BIA 2-194 (S-licarbazepine), the major metabolite.

The results of the study in children and adolescents revealed that the extent of absorption and metabolism might be age dependant as clearance is decreased in older children. The clearance in younger children appears to be increased.

These issues will be clarified in the paediatric clinical programme which is ongoing.
BIAL received in December 2006 Scientific Advice from EMEA with respect to the use of Exalief in paediatric patients. In June 2007, BIAL received from EMEA Scientific Advice regarding a waiver request for a non clinical study in juvenile animals with Exalief. The final study report from the therapeutic exploratory study [Study No. BIA-2093-202], "Pharmacokinetics, efficacy and tolerability of Exalief in children and adolescents with refractory partial epilepsy", was included in the original MAA.
The study comprises use of Exalief in children and adolescents 2-17 years with partial onset seizures not controlled in spite of treatment with one to three current AEDs. A randomised, placebo-controlled Phase III study (Study No. BIA-2093-305) in paediatric patients (2-16 years) with partial-onset seizures refractory to treatment with one or two other AEDs is ongoing and 92 patients out of 252 planned were enrolled by the 3rd September 2008.
A study aiming to evaluate the effect of Exalief on cognitive function in children 6-16 years old is planned to start during the 4th quarter of 2008 (Study No. BIA-2093-208). BIAL plans to submit a PIP of the use of Exalief in children with partial onset seizures to EMEA during the 2nd -3rd quarter of 2009.

Pharmacokinetics Interaction studies

Pharmacokinetic interactions between Exalief and digoxin, warfarin, oral contraceptives, phenytoin, topiramate and lamotrigine have been investigated.

In particular, the interaction with other AEDs has been investigated in three dedicated drug interaction studies, [BIA 2093-119] with lamotrigine (LMT), [BIA 2093-120] with topiramate (TPM) and [BIA 2093-121] with phenytoin (PHT), and from analysis of data from the Phase III programme [Studies 301, 302 and 303].

Increased plasma levels were only found with phenytoin. In summary, the conclusions from the findings of these studies are as follows:

Phenytoin
At steady state (BIA-2093-121) the total exposure of BIA 2-194 was reduced if phenytoin was concomitantly applied. Enzyme induction is a possible explanation.
Exalief increased plasma levels of phenytoin at steady state, probably due to inhibition of CYP2C19 and in accordance with this finding a higher incidence of adverse events was observed.

Topiramate
Topiramate had no clinical relevant impact on the pharmacokinetics of Exalief at steady state (BIA-2093-120). However Exalief reduced the total exposure of topiramate about 20%. The concomitant administration of topiramate and Exalief did not increase the incidence of adverse effects.

Lamotrigine
An interaction study (BIA-2093-119) of lamotrigine and Exalief showed no pharmacokinetic interaction at steady state.

The following table summarises results of the effect of Exalief on other AEDs from all the mentioned sources. It also includes a column with a plausible mechanism for identified interactions, and a column with the effect of OXC (Trileptal) on other AEDs as reference.

Effect of ESL on other Anti Epileptic Drugs (AED)

AED	Dedicated interaction studies BIA 2093-119 BIA 2093-120 BIA 2093-121	Bioequivalence approach of sparse data Memo-ESL-AEDs DDIsPhIII-20APR2007	POP PK of sparse Phase III data EMFFR2007/10/01	Plausible mechanism	OXC (approved label)
Phenytoin (PHT)	35%↑ of PHT exposure	11% ↑ of PHT exposure at ESL 800 mg, no data for > doses	No effect on PHT	Inhibition of CYP2C19	40% ↑ of PHT exposure at OXC doses >1200 mg/day
Phenobarbi-tal (PHB)		41% increase of PHB exposure at ESL 1200 mg	No effect on PHB	Inhibition of CYP2C19	14% ↑ of PHB exposure
Lamotrigine (LMT)	14% ↓ of LMT exposure	ESL QD 25% ↓ of LMT exposure, ESL BID 55% ↓ of LMT	12% ↑ in clearance of LMT	No interaction	
Topiramate (TPM)	18% ↓ of TPM exposure	16% ↓ of TPM exposure	5-16% ↑ in clearance of TPM, 3-8.5% ↑ in clearance if also on CBZ	Mechanism unknown but reduced bioavailability is a plausible explanation.	
Levetirace-tam (LEV)		No effect on LEV	No effect on LEV	No interaction	
Carbamaze-pine (CBZ)		13% ↓ of CBZ exposure	Up to 14%↑ in CBZ clearance at 200 mg dose. Effect lower at higher CBZ doses due to ↑ auto--induction	Induction of CYP3A4.	<10% ↓ of CBZ exposure
Valproate (VPT)		No effect on VPT	No effect on VPT	No interaction	<10% ↓ of VPT exposure

Analogously, the results of the effect of other AEDs on Exalief is provided in the following table. It also includes a column with plausible mechanism for identified interactions, and a column with the effect of AEDs on OXC as reference.

Effect of other Anti Epileptic Drugs (AEDs) on ESL

AED	Dedicated interaction studies BIA 2093-119 BIA 2093-120 BIA 2093-121	POP PK of sparse data + rich data PK sub-study of BIA 2093-301 EMFFR2007/13 /00	POP PK of sparse Phase III data EMFFR2007/09/01	Plausible mechanism	OXC (approved label)
Phenytoin (PHT)	33 % ↓ of eslicarbazepine exposure	33% ↑ in CL of eslicarbazepine by PHT /PHB.	60% ↑ in CL of ESL by barbiturates	Induction of glucuroni-dation	30% ↓ of MHD exposure
Phenobarbi-tal (PHB)					25% ↓ of MHD exposure
Lamotrigine (LMT)	No effect on eslicarbazepine.		No effect on eslicarbazepine	No interaction	
Topiramate (TPM)	10% ↓ of eslicarbazepine exposure		No effect on eslicarbazepine	No interaction	
Levetirace-tam (LEV)			No effect on eslicarbazepine	No interaction	
Carbamaze-pine (CBZ)		40% ↑ in CL of ESL	13% ↑ in CL of eslicarbazepine at 200 mg CBZ dose, 150% ↑ in CL at 2400 mg CBZ dose.	Dose dependent induction of glucuroni-dation	40% ↓ of MHD exposure
Valproate (VPT)			No effect on eslicarbazepine	No interaction	18% ↓ of MHD exposure

These summary tables indicate that results obtained from the different sources are in good agreement with each other, both with regard to the effect of Exalief on the PK of other AEDs and the effect of other AEDs on the PK of eslicarbazepine. Results are also in line with the known interaction profile of OXC, which could be expected considering the qualitative similarities between Exalief and OXC, with eslicarbazepine and R-licarbazepine being the main circulating compounds for both although the relative ratio differs.
Overall, the magnitudes of the effect of Exalief on concomitant AEDs are small and would not justify dose adjustments except when combined with PHT. The increase in exposure to PHT, which probably is caused by inhibition of its metabolism via CYP2C19, seems to be dose dependent and dose adjustments may only be indicated at Exalief doses exceeding 800 mg per day. Barbiturates also have an effect on Exalief, with a 30-60 % reduction in drug exposure. A similar effect is also seen with carbamazepine (CBZ), the probable mechanism being a dose dependent induction of glucuronidation. No clinically relevant effects on Exalief were found with LMT, TPM, levetiracetam or valproate.

Interaction with other drugs

Digoxin
Concomitant administration of Exalief had no relevant effect on the extent of systemic exposure to Digoxin (as expressed by Digoxin AUCτ). With respect to the rate of systemic exposure, concomitant administration of Exalief decreased Cmax of Digoxin by 15%, which is not expected to affect the therapeutic efficacy. Saftey should not be affected negatively.

Warfarin
Co-administration of Exalief 1200 mg QD with warfarin showed a significant decrease in exposure to S-warfarin, with no significant effect on the R-warfarin pharmacokinetics; since S-warfarin clearance is mediated almost entirely by CYP2C9, whereas R-warfarin clearance is dependent on multiple CYP pathways (CYP2C19, CYP3A4 and CYP1A2).

Oral contraceptives
Administration of Exalief to female subjects showed a decrease in systemic exposure to both hormones of a combined oral contraceptive containing levonorgestrel and ethinyloestradiol. Therefore, it must be considered that concurrent use of Exalief and hormonal contraceptives may render the contraceptives less effective.

- Pharmacokinetics using human biomaterials

In *in vitro* studies in human liver microsomes, Eslicarbazepine appeared to have no relevant inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4 and CYP2C9 and only a moderate inhibitory effect on CYP2C19. The 50% inhibitory concentration (IC50) values for Eslicarbazepine upon CYP2C19 activity were 232 µg/mL. Studies with Eslicarbazepine in fresh human hepatocytes showed no significant induction of CYP1A2, CYP3A and phase 2 enzymes involved in glucuronidation and sulphatation of 7-hydroxy-coumarin. The incubation of 14C-BIA 2-093 in the presence of AEDs acetazolamide, clobazam, clonazepam, gabapentin, LMT, phenobarbital, PHT, primidone and sodium valproate showed no relevant inhibition of Exalief metabolism by these AEDs.

Pharmacodynamics

Introduction

Eslicarbazepine acetate (Exalief) represents a third-generation, single enantiomer member of the well-known family of first-line dibenz[b,f]azepine antiepileptic drugs carbamazepine (CBZ, first generation) and oxcarbazepine (OXC, second generation).

Mechanism of action

Although the precise mechanism of action is unknown, electrophysiological studies indicate that both Exalief and its active metabolites (S-licarbazepine, R-licarbazepine and oxcarbazepine) stabilize the inactivated state of voltage-gated sodium channels (site 2). Therefore, Exalief is supposed to act as a voltage-gated sodium channel blocker.

Primary pharmacology

For epilepsy there is no human pharmacodynamic model. Therefore, no specific pharmacodynamic models have been evaluated during Phase I clinical studies.
The primary pharmacodynamic *in vivo* and *in vitro* animal studies were directed at examining the anticonvulsive properties of Exalief and its metabolites. Using well-known models for testing anticonvulsive activity (maximal electroshock, corneal kindling, different chemoconvulsant tests) Exalief was found to display qualitatively the same anticonvulsive profile as the comparator CBZ.

Secondary pharmacology

Thorough QT- study

The study results did not raise concerns with respect to a QTc prolonging potential. Moxifloxacin established the assay sensitivity. The numerical small increase in QTcB is not considered relevant.

Despite of a mild increase in heart rate the PR interval increases dose dependently with Eslicarbazepine acetate by about 5 – 8 ms (placebo: 2 ms). This is neither considered of clinical relevance on its own.

The outlier analysis did not indicate a clear dose effect for Eslicarbazepine acetate. Due to statistical reasons the negative predictive value of the outlier analysis is limited, however.

With respect to safety ECGs the analysis did not show dose dependent ECG abnormalities.
In summary, the thorough QT study did not raise concerns with respect to QT-prolongation.

CLINICAL EFFICACY

Introduction

The clinical development program of Exalief as adjunctive oral (tablet) therapy in adult subjects with partial onset seizures includes the following completed Phase II and Phase III clinical trials:

- 1 completed double-blind Phase II supporting trial (BIA-2093-201),
- 3 primary double-blind, placebo controlled efficacy trials (part I of BIA-2093-301, BIA-2093-302 and BIA-2093-303, respectively) and
- 1 open label extension study evaluating long-term efficacy and safety of Exalief (part II of BIA-2093-301).

Three open-label extention studies in the sought indication were still ongoing at the time of the submission: part II of BIA-2093-302 and BIA-2093-203, respectively as well as part III of BIA-2093-301.

These studies are summarised in the following table:

Study ID	Trial Design	ESL dose/day	Maximum treatment duration (verum)	Total number of subjects
Primary efficacy trials				**Randomized (Completed)**
BIA-2093-301 (part I)	mc, db, pc	400, 800 or 1200 mg	16 weeks (12 week maintenance period)	402 (330)
BIA-2093-302 (part I)	mc, db, pc	400, 800 or 1200 mg	14 weeks (12 week maintenance period)	395 (327)
BIA-2093-303 (part I)	mc, db, pc	800 or 1200 mg	16 weeks (12 week maintenance period)	253 (197)
Supporting efficacy trial				**Randomized (Completed)**
BIA-20932093-201	mc, db, pc	400 to 1200 mg	13 weeks (12 week maintenance with increasing doses)	144 (110)
Long-term efficacy trials				**Treated with ESL**
Part II of BIA-2093-301	ole	400 to 1200 mg	1 year *	314 patients (239 patients completed study)
Part II of BIA-2093-302 (ongoing)	ole	400 to 1200 mg	1 year*	519 subjects exposed in ongoing open label extension studies (as of 30 September 2007)
Part II of BIA-2093-303 (ongoing)	ole	400 to 1200 mg	1 year	
Part III of BIA-2093-301 (ongoing)	ole	400 to 1200 mg	1 year	

mc= multicenter, db=double blind, pc=placebo controlled, ESL=Eslicarbazepine acetate
ole= open label extension
* after completion of part II, patients had/have the opportunity to enter a further extension period, part III of respective study (ongoing)

The three phase III studies were pooled and a pre-planned analysis was performed (Phase III integrated studies).

In addition to the studies performed in the indication applied for, one phase II study in children with epilepsy (Study No. BIA-2093-202) and three phase II studies in adult patients with bipolar disorder (Study Nrs. BIA-2093-203, -204 and -205, respectively) have been conducted.

Dose-response studies and main clinical studies

The doses used to evaluate the efficacy of Exalief in the phase 2/3 trials were derived from phase I and one phase II studies which showed therapeutic properties and an acceptable safety profile of 800 mg and 1200 mg Exalief as adjunctive therapy in a once-daily regimen, and a smaller treatment response for the 400 mg dose. The phase III studies were planned to define the dose recommendations to be included in the SPC.

Based on these results, Exalief 400 mg (except in study BIA-2093-303), 800 mg and 1200 mg were investigated in the phase II and III studies in the claimed indication.

Main studies

Studies BIA-2093-301, BIA-2093-302 and BIA-2093-303 (referred to as studies 301, 302 and 303, respectively) and phase III integrated studies

Methods

The 3 pivotal studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303, respectively) were similar in design:

They were 2-part, multicenter, randomised, double-blind, placebo-controlled studies in subjects with refractory simple or complex partial-onset seizures, with or without secondarily generalisation. Seizures were classified according to the International Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Part I of each study followed a parallel-group design and consisted of a 8-week prospective baseline period (single-blind placebo period in study 301 only), followed by a double-blind 2-week titration period, a double-blind 12-week maintenance period, and in studies 301 and 303, a double-blind 4-week tapering-off period.

Table: Study design and treatment regimens for Phase III efficacy studies

Study	No. Subjects Randomised	Study Design	Treatment Regimen
BIA-2093-301 BIA-2093-302 BIA-2093-303	402 395 253	**Part I:** 26-week, parallel-group, randomised, placebo-controlled study (22 weeks in Study 302): – 8-week baseline period (in Study 301: single-blind placebo period) – 2-week double-blind titration period – 12-week double-blind maintenance period – 4-week double-blind tapering-off period (not in Study 302) **Part II:** Optional, 1-year, open-label extension for subjects who had completed Part I.	**Part I:** – Placebo – Daily doses of ESL: – Studies 301 + 302 = 400, 800 or 1200 mg (QD) – Study 303 = 800 or 1200 mg (QD) **Part II:** Starting dose of 800 mg ESL QD that could be titrated up or down at 400-mg intervals between 400 and 1200 mg

QD = once daily

The only major differences between the 3 studies in the Part I study design were the doses of ESL given and differences in the study periods and titration regimens:

- There were 3 ESL dose groups (400 mg, 800 mg or 1200 mg once daily [QD]) in studies 301 and 302, but only 2 ESL dose groups (800 mg or 1200 mg QD) in study 303.
- The baseline period was observational in studies 302 and 303 and single-blind placebo in study 301.
- In study 302 there was no tapering-off period.
- All 3 studies used slightly different titration and tapering-off regimens.

Part II of each study was an optional 1-year open-label period of treatment with Exalief for those subjects who completed the 12-week maintenance period in study 302 and the 4-week tapering-off period in studies 301 and 303.

As predefined in the study protocol of each phase III study, the data of part I of the three phase III studies were pooled and a pre-planned analysis was performed in order to describe the efficacy and safety of Exalief in as broad a population as possible (Phase III integrated studies). This is acceptable as the studies are similar in design.

- Study Participants

Key **inclusion criteria** for each of the 3 studies were:

At Visit 1 (screening), subjects must have:

- Been 18 years or older.
- Had a documented diagnosis of simple or complex partial seizures with or without secondary generalisation for at least 12 months prior to screening.
- Had at least 4 partial seizures in each 4-week period during the last 8 weeks prior to screening.
- Been currently treated with 1 or 2 AEDs[1] (any except oxcarbazepine and felbamate), in a stable dose regimen for at least 2 months prior to screening (subjects using vigabatrin should have been on this medication for at least 1 year with no deficit in visual field identified, and a confirmatory test should be available within 1 month before study entry; if present, VNS was considered an AED, i.e. only 1 concomitant AED was allowed in subjects with VNS).

[1]In Study 302, the number of allowed concomitant AEDs was extended to 3 AEDs by amendment.

At Visit 2 (randomisation), subjects must have:

- Had at least 4 partial seizures in each 4-week period of the 8-week baseline period prior to randomisation (documented in a diary) and no seizure-free interval exceeding 21 consecutive days.
- Satisfactorily completed diaries by themselves or their caregiver.
- Satisfactorily complied with the study requirements during the baseline period.

Key **exclusion criteria** for each of the 3 studies included if a subject had:

- Only simple partial seizures with no motor symptomatology (classified as A2-4 according to the International Classification of Epileptic Seizures) that were not video-electroencephalogram documented.
- Primary generalised epilepsy.
- Known rapid progressive neurological disorder.
- A 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 psychogenic origin within the last 2 years.
- A history of schizophrenia or suicide attempt.
- Exposure to felbamate or oxcarbazepine within 1 month of screening.
- Exposure to benzodiazepines on more than an occasional basis (except when used chronically as AED).

- Known hypersensitivity to carbamazepine, oxcarbazepine, or chemically related substances.
- Second or third-degree atrioventricular blockade not corrected with a pacemaker
- Relevant clinical laboratory abnormalities (e.g. Na^+ <130 mmol/L, ALT or AST >2.0 times the upper limit of normal, WBC count <3,000 cells/mm^3).
- An estimated creatinine clearance (CL_{CR}) <50 mL/min.

- Treatments

During the 8 week baseline period of study 301, placebo was administered QD in a single-blind fashion, which should allow for an accounting of the number of seizures under placebo treatment.

In studies 302 and 303, no study treatment was administered during baseline.
At the end of the baseline period, subjects who met the selection criteria were randomly assigned to 1 of the following treatment groups, study medication was taken without regard to meals:

• **Studies BIA-2093-301 and BIA-2093-302:**	• **Study BIA-2093-303:**
randomisation ratio: 1:1:1:1	randomisation ratio: 1:1:1
• Group 1: ESL 1200 mg	• Group 1: ESL 1200 mg
• Group 2: ESL 800 mg	• Group 2: ESL 800 mg
• Group 3: ESL 400 mg	• Group 3: Placebo
• Group 4: Placebo	

The dosing schedules for the different periods are illustrated below:

Group 1: ESL 1200 mg

Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
301	Placebo	Week 1: 400 mg Week 2: 800 mg	1200[a] mg	Week 15: 800 mg Week 16: 400 mg Weeks 17+18: Placebo
302	No treatment	800 mg	1200[a] mg	Not applicable
303	No treatment	600 mg	1200[b] mg	Weeks 15+16: 600 mg Weeks 17+18: Placebo

[a] 1x 400 mg plus 1 x 800 mg tablets

[b] 2 x 600 mg tablets

Group 2: ESL 800 mg

Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
301	Placebo	Week 1: 400 mg Week 2: 800 mg	800 mg	Week 15: 800 mg Week 16: 400 mg Weeks 17+18: Placebo
302	No treatment	800 mg	800 mg	Not applicable
303	No treatment	400 mg	800 mg	Weeks 15+16: 400 mg Weeks 17+18: Placebo

Group 3: ESL 400 mg

Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
301	Placebo	400 mg	400 mg	Weeks 15+16: 400 mg Weeks 17+18: Placebo
302	No treatment	400 mg	400 mg	Not applicable
303	Not applicable			

Group 4: Placebo

Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
301	Placebo	Placebo	Placebo	Placebo
302	No treatment	Placebo	Placebo	Not applicable
303	No treatment	Placebo	Placebo	Placebo

- Objectives

The 3 pivotal studies had essentially the same objectives:

The primary study objective was to evaluate the efficacy of Exalief administered once daily at doses of 400 mg[1], 800 mg and 1200 mg compared with placebo as adjunctive therapy in patients with refractory partial epilepsy over a 12-week maintenance period.

The secondary objectives of this study were the following:

- To evaluate the safety and tolerability of Exalief at once-daily doses of 400 mg[1], 800 mg and 1200 mg in comparison to placebo, over a 12-week maintenance period preceded by a 2-week titration period and followed by a 4-week tapering-off period[2] .
- To evaluate the safety and tolerability of Exalief at doses titrated to an efficacy or safety endpoint over a 1-year open-label period.
- To assess the maintenance of therapeutic effects of Exalief over a 12-week maintenance period preceded by a 2-week titration period and followed by a 4-week tapering-off period[2] and over a 1-year open-label period.

- To assess the drug-drug pharmacokinetic interactions between Exalief and concomitant AEDs over the double-blind and open-label parts of the study.
- To assess the health-related quality-of-life and depressive symptoms over the double-blind and open-label parts of the study.

[1] only in study 301 and 302
[2] only studies 301 and 303 had a tapering period

- Outcomes/endpoints

In all three pivotal studies, the primary efficacy endpoint was:

seizure frequency over the 12-week maintenance period in Part I of the study, standardised to a 'frequency per 4 weeks' unit.

Secondary efficacy endpoints were as follows:

- Proportion of responders (i.e., patients with a ≥ 50% reduction in seizure frequency during the 12-week maintenance period compared with the 8-week baseline period)
- Seizure frequency per week for each week of the baseline, titration, maintenance, and tapering-off periods (the latter except study 302, which had no tapering-off period)
- Distribution of seizure reduction (< 50%, 50-75%, or >75% seizure reduction)
- Proportion of seizure-free patients (100% seizure reduction)
- Proportion of patients with a 25% or greater exacerbation in seizure frequency compared to baseline
- Seizure frequency by seizure type
- Seizure frequency as a function of BIA 2-194 plasma levels at visit 5
- Treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]) during Part I of the study
- Clinical global impressions (CGIs)
- Responses to the Quality of Life in Epilepsy-31 inventory (Quolie-31)
- Symptoms of depression (based on Montgomery Asberg Depression Rating Scale [MADRS]).

Safety: Safety endpoints included AEs, clinical laboratory tests (hematology, coagulation, biochemistry, and thyroid function, urin alaysis), vital signs and weight, electrocardiogram, blood trough levels of concomitant AEDs, and withdrawal and/or rebound effect during the tapering-off period (the latter except study 302, which had no tapering-off period).

Phase III integrated studies:

The primary efficacy variable in the integrated analyses was the standardised seizure frequency over the 12-week maintenance period, which was also the primary efficacy variable in each of the individual studies. In addition, for the integrated analysis there were 2 key secondary variables for the assessment of efficacy of Exalief compared to placebo:

- Frequency of responders (≥ 50% reduction in seizure frequency from the 8-week baseline period to the 12-week maintenance period).
- Relative reduction (%) in seizure frequency from the 8-week baseline period to the 12-week maintenance period.

Several other secondary efficacy variables were also analysed for the 12-week maintenance period, including:

- Relative reduction in seizure frequency and responder rate per week
- Categorised relative change in seizure frequency (seizure reduction <50%, 50% to 75% and >75%, exacerbation <25% and ≥25%)
- Most severe type of seizure by week
- Number of days with seizures
- Proportion of seizure-free subjects (100% seizure reduction)

- Treatment retention time (time to withdrawal due to lack of efficacy or adverse events) in Part I of the study
- Changes in the Clinical Global Impression (CGI), Montgomery Asberg Depression Rating Scale (MADRS) and the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) questionnaires
- The effect on the seizure frequency (primary efficacy variable) due to an interaction between Exalief and concomitantly given AEDs

The following were analysed as other secondary efficacy variables for the titration and tapering-off periods: Standardised seizure frequency and relative reduction of standardised seizure frequency.

- Sample size

In all three pivotal studies samples size determinations and statistical powering calculations were based on the primary efficacy variable (natural log transformation of the seizure frequency in a 4-week period).
Assuming that approximately 15% of the randomised patients would be excluded from the efficacy population, the required number of patients to be recruited in total was approximately 400 for studies 301 and 302 and 252 for study 303.

- Randomisation

All pivotal studies were randomised and double-blind. The randomisation procedure appears adequate. In studies 301 and 302, patients were randomized in a 1:1:1:1 ratio to placebo, Exalief 400 mg/day, Exalief 800 mg/day or Exalief 1200mg/day, respectively; in study 303, patients were randomized in a 1:1:1 ratio to placebo, Exalief 800 mg/day or Exalief 1200 mg/day, respectively.

- Blinding (masking)

Studies 301 and 302:
Exalief was presented as white oblong tablets of 400 mg and 800 mg. As the 800 mg tablet is thicker than the 400 mg tablet, matching placebo tablets were available for both strengths of Exalief.

Study 303:
Exalief was presented as white oblong tablets of 400 mg and 600 mg which were of the same size and appearance; matching placebo tablets were used.

The investigator was provided with a sealed envelope for each patient containing information about the study medication administered to the patient. The envelope might only be opened in case of emergency, when knowledge of the treatment was needed. Decoding had to be documented and at the end of the study, all envelopes had to be returned to the sponsor via CRO.

- Statistical methods

The statistical methods were essentially the same for the three pivotal studies:

Safety population: The safety population consisted of all patients, who received at least 1 dose of the investigational product after randomisation.

Intention-to-treat (ITT): The ITT population consisted of all randomised patients, with at least one administration of the investigational product and at least one post-baseline seizure frequency assessment. If a patient discontinued before the end of the 12-week maintenance period then all data from the start of the 2-week titration period to discontinuation were used. If the variable was a summarisation of the 12-week maintenance period then only data from the start of the maintenance period to discontinuation were used. If the variable was a summarisation of the 12-week maintenance

period and the titration period then all data from the start of the titration period to discontinuation were used.

Per-protocol (PP): The PP efficacy population included all patients completing the 12-week maintenance period of the study and without major protocol violations.
Assignment of patient to ITT and PP populations were undertaken by a blinded review of the data prior to database lock.

The primary efficacy assessment was based on an ITT approach. All primary and secondary efficacy variables were also analysed for the PP population.

Seizure frequency was compared among the treatment groups by using an analysis of covariance (ANCOVA) that models seizure frequency as a function of baseline seizure frequency and treatment. Natural logarithm transformation was applied to standardised seizure frequency in order to conform to the assumptions of ANCOVA and to be consistent with sample size calculation. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean. The proportion of responders over the 12-week maintenance period was analysed by using a Cochran-Mantel-Haenszel (CMH) test. Continuous data were summarised by using descriptive statistics, i.e., number of patients, mean, standard deviation, median, and range (minimum and maximum). Categorical variables were summarised by using frequency (counts) and percentages. By-patient data listings were prepared in support of all statistical summary tables and for other case report form data, as appropriate. For testing the differences the following tests were used: Least square means from the ANCOVA for each treatment group (adjusted for the covariates), least square means for differences between each active dose and placebo.
Dunnett p-values and confidence intervals (CIs) for those differences were presented when ANCOVA or analysis of variance test were used.

Results

- Participants

In the 3 Phase III studies combined, 1050 subjects were randomized and 1049 (99.9%) began treatment in the titration period, the ITT population comprised 1035 (98.6%), the PP population 756 (72.0%) patients.
The following table presents the study populations in each study and each treatment goup:

Table: Analysis populations - Phase III integrated studies

Population	Number (%) of Subjects					
	Placebo	ESL				Overall
		400 mg	800 mg	1200 mg	Total	Total
Study BIA-2093-301						
Randomised	102	100	98	102	300	402
Safety[a]	102 (100)	100 (100)	98 (100)	102 (100)	300 (100)	402 (100)
ITT[b]	102 (100)	99 (99.0)	98 (100)	98 (96.1)	295 (98.3)	397 (98.8)
Per protocol[c]	91 (89.2)	94 (94.0)	86 (87.8)	72 (70.6)	252 (84.0)	343 (85.3)
Study BIA-2093-302						
Randomised	100	96	101	98	295	395
Safety[a]	100 (100)	96 (100)	101 (100)	98 (100)	295 (100)	395 (100)
ITT[b]	100 (100)	96 (100)	100 (99.0)	97 (99.0)	293 (99.3)	393 (99.5)
Per protocol[c]	81 (81.0)	70 (72.9)	75 (74.3)	54 (55.1)	199 (67.5)	280 (70.9)
Study BIA-2093-303						
Randomised	88	0	85	80	165	253
Safety[a]	87 (98.9)	0	85 (100)	80 (100)	165 (100)	252 (99.6)
ITT[b]	84 (95.5)	0	84 (98.8)	77 (96.3)	161 (97.6)	245 (96.8)
Per protocol[c]	51 (58.0)	0	47 (55.3)	35 (43.8)	82 (49.7)	133 (56.6)
Integrated Analysis						
Randomised	290	196	284	280	760	1050
Safety[a]	289 (99.7)	196 (100)	284 (100)	280 (100)	760 (100)	1049 (99.9)
ITT[b]	286 (98.6)	195 (99.5)	282 (99.3)	272 (97.1)	749 (98.6)	1035 (98.6)
Per protocol[c]	223 (76.9)	164 (83.7)	208 (73.2)	161 (57.5)	533 (70.1)	756 (72.0)

ITT = intent-to-treat.

[a] Subjects who had taken at least 1 dose of randomised study medication.

[b] All randomised subjects with at least 1 administration of study medication and at least 1 post-baseline seizure frequency assessment, i.e. at least 1 subject diary was available.

[c] All subjects completing the 12-week maintenance period of the study without major protocol violations.

The percentage of subjects who completed titration and maintenance periods, respectively is shown in the following table:

Table: Study completion status - Phase III integrated studies

Disposition	Number (%) of Subjects				
	Placebo	ESL			
		400 mg	800 mg	1200 mg	Total
Randomised	290	196	284	280	760
Titration period					
Started	289 (100)	196 (100)	284 (100)	280 (100)	760 (100)
Completed	285 (98.6)	194 (99.0)	270 (95.1)	263 (93.9)	727 (95.7)
Maintenance period					
Started	280 (96.9)	192 (98.0)	263 (92.6)	253 (90.4)	708 (93.2)
Completed	259 (89.6)	178 (90.8)	240 (84.5)	201 (71.8)	619 (81.4)

Most discontinuations were because of unacceptable AEs which occurred in a treatment- and dose-dependent manner, followed by 'other reason', withdrawal of consent and patient non-compliance.
The percentage of patients discontinuing treatment increases noticeably with increasing dose. Whereas the percentage of withdrawals across all three studies is essentially similar in the placebo and 400 mg dose group, it is higher in the 800 mg dose group and is almost double as high in the highest dose group (1200 mg) compared to the 800 mg dose group. Most discontinuations were because of unacceptable AEs which occurred in a treatment- and dose-dependent manner. In all 3 single studies these findings were alike.

- Conduct of the study

In study 301 no amendments to the final study protocol relevant to part I were issued.
In study 302, among 3 protocol amendments, one is of interest: as inclusion criterion, the number of allowed concomitant AEDs was extended from 2 to 3.

In study 303, among 2 protocol amendments, one is mentionable: to reach the recruitment goal 14 study sites in Mexico were opened (in addition to the centres in Portugal and Spain).

The number of concomitant AEDs is optimally 1 or 2. However, only 8.1 % of the ITT population of study 302 and <5% of the safety population of the phase III integrated studies took three concomitant AEDs.

- Baseline data

Phase III integrated studies
The combined population was predominantly Caucasian (76.8% in the placebo group, 81.3% in the Total Exalief group) and approximately 20% Hispanic in each group (except for the 400 mg Exalief group since Study 303 did not have a 400 mg group and was the only study to include Mexico), see following table.

Table: Demographic and other baseline characteristics - Phase III integrated studies (safety population)

Characteristic	Placebo	ESL			
	(N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total (N=760)
Age					
Mean±SD	36.9±12.01	37.5±11.26	38.0±11.96	37.0±11.54	37.5±11.62
n (%) <18 years	2 (0.7)	0	0	1 (0.4)	1 (0.1)
n (%) ≥65 years	5 (1.7)	2(1.0)	3 (1.1)	4 (1.4)	9 (1.2)
Gender					
Male	143 (49.5)	89 (45.4)	140 (49.3)	131 (46.8)	360 (47.4)
Female	146 (50.5)	107 (54.6)	144 (50.7)	149 (53.2)	400 (52.6)
Ethnic group, n (%)					
Caucasian	222 (76.8)	187 (95.4)	221 (77.8)	210 (75.0)	618 (81.3)
Hispanic	54 (18.7)	2 (1.0)	52 (18.3)	53 (18.9)	107 (14.1)
African (black)	8 (2.8)	2 (1.0)	6 (2.1)	9 (3.2)	17 (2.2)
Other	5 (1.7)	3 (1.5)	4 (1.4)	3 (1.1)	10 (1.3)
Asian	0	2 (1.0)	1 (0.4)	5 (1.8)	8 (1.1)
BMI					
n (%)	288 (99.7)	196 (100)	283 (99.7)	280 (100)	759 (99.9)
Mean±SD	25.2±4.45	24.6±4.63	24.9±4.61	25.5±4.70	25.1±4.66
Missing	1 (0.3)	0	1 (0.4)	0	1 (0.1)

N = total number of subjects; n = number of subjects with available data; SD = standard deviation.

Only very few patients of the pivotal studies were ≥65 years (9 patients (1.2 %) in the total Exalief and 5 patients (1.7%) in the placebo group, respectively.

Baseline disease characteristics at baseline were similar in each of the treatment groups (see following table).

Table: Baseline disease characteristics - Phase III integrated studies (safety population)

Characteristic	Placebo	ESL			
		400 mg	800 mg	1200 mg	Total
	(N=289)	(N=196)	(N=284)	(N=280)	(N=760)
Duration of epilepsy					
Mean±SD	22.7±13.11	22.8±11.98	22.6±12.30	22.0±12.52	22.4±12.29
Age at onset					
Mean±SD	14.1±12.31	14.7±12.36	15.4±13.42	15.0±12.64	15.0±12.85
Family history, n (%)					
Yes	31 (10.7)	8 (4.1)	33 (11.6)	20 (7.1)	61 (8.0)
No	257 (88.9)	187 (95.4)	251 (88.4)	260 (92.9)	698 (91.8)
Missing	1 (0.3)	1 (0.5)	0	0	1 (0.1)
Possible aetiologies, n (%)					
Idiopathic	78 (27.0)	33 (16.8)	64 (22.5)	67 (23.9)	164 (21.6)
Congenital/ hereditary disorders	25 (8.7)	20 (10.2)	26 (9.2)	29 (10.4)	75 (9.9)
Cranial trauma/ injuries	39 (13.5)	36 (18.4)	33 (11.6)	30 (10.7)	99 (13.0)
Systemic/toxic/ metabolic disorders	4 (1.4)	3 (1.5)	3 (1.1)	4 (1.4)	10 (1.3)
Infectious diseases	22 (7.6)	27 (13.8)	29 (10.2)	33 (11.8)	89 (11.7)
Brain tumours	12 (4.2)	4 (2.0)	9 (3.2)	6 (2.1)	19 (2.5)
Cerebrovascular diseases	5 (1.7)	3 (1.5)	8 (2.8)	12 (4.3)	23 (3.0)
Other/unknown	104 (36.0)	75 (38.3)	113 (39.8)	103 (36.8)	291 (38.3)

N = total number of subjects; n = number of subjects with data available; SD = standard deviation.

Mean standardised seizure frequency at baseline was about 13 seizures/28 days in all treatment groups, the most frequent seizures were complex partial seizures, followed by simple partial seizures. Mean standardised seizure frequency of secondary generalised or unclassified seizures was considerably lower. The frequency of each seizure type was similar in each of the treatment groups (see following table).

Table: Baseline standardised seizure frequency - Phase III integrated studies (safety population)

Seizure Type	Placebo	ESL			
	(N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total (N=760)
Overall seizures					
n (%)	287 (99.3)	196 (100)	284 (100)	277 (98.9)	757 (99.6)
Mean±SD	12.9±16.77	13.0±15.05	13.4±15.26	13.1±15.11	13.2±15.13
Simple Partial					
n (%)	138 (47.8)	87 (44.4)	138 (48.6)	133 (47.5)	358 (47.1)
Mean±SD	4.9±11.24	5.1±13.09	5.5±11.64	4.8±10.03	5.2±11.47
Complex Partial					
n (%)	197 (68.2)	139 (70.9)	207 (72.9)	204 (72.9)	550 (72.4)
Mean±SD	5.6±12.14	5.7±7.98	6.1±9.65	6.1±11.78	6.0±10.11
Partial Evolving					
n (%)	92 (31.8)	66 (33.7)	86 (30.3)	91 (32.5)	243 (32.0)
Mean±SD	1.3±3.86	1.3±3.48	1.1±2.99	1.2±3.44	1.2±3.29
Unclassified					
n (%)	45 (15.6)	21 (10.7)	46 (16.2)	43 (15.4)	110 (14.5)
Mean±SD	1.0±4.52	0.8±4.93	0.7±3.00	1.1±4.33	0.8±4.07

N = total number of subjects; n = number of subjects with data available; SD = standard deviation.

The majority (about 70%) of patients used 2 concomitant AEDs in each of the treatment groups followed by 1 concomitant AED (22.5% - 31.1%).

Table: Number of concomitant anti-epileptic drugs taken in parallel at end of the baseline period - Phase III integrated studies (safety population)

Number of AEDs	Number (%) of subjects				
	Placebo	ESL			
	(N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total (N=760)
0	0	1 (0.5)	0	0	1 (0.1)
1	65 (22.5)	61 (31.1)	72 (25.4)	73 (26.1)	206 (27.1)
2	210 (72.7)	129 (65.8)	199 (70.1)	197 (70.4)	525 (69.1)
3	14 (4.8)	4 (2.0)	12 (4.2)	9 (3.2)	25 (3.3)
4	0	1 (0.5)	1 (0.4)	1 (0.4)	3 (0.4)

AED = anti-epileptic drug.

The percentage of patients taking only 1 concomitant AED was somewhat higher in the 400 mg dose group compared to placebo group, and was evenly distributed in the placebo, 800 and 1200 mg dose

groups. This is not to be regarded of relevance, as it seems to privilege the 400 mg dose group. However, the 400 mg dose group did not prove to be efficacious. A similar finding was seen for study 302. The number of concomitant AEDs in studies 301 and 303 was inconspicuous.

The most frequent concomitant AEDs were Carbamazpine, Valproic acid and Lamotrigine in all three single studies. Concomitant AEDs used by more than 1% of study patients at baseline are given in the following table:

Table: Most frequent concomitant anti-epileptic drugs at the end of the baseline period - Phase III integrated studies (safety population)

AED	Number (%) of subjects				
	Placebo	ESL			
	(N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total (N=760)
Carbamazepine	181 (62.6)	114 (58.2)	162 (57.0)	153 (54.6)	429 (56.4)
Valproic acid	82 (28.4)	37 (18.9)	74 (26.1)	72 (25.7)	183 (24.1)
Lamotrigine	63 (21.8)	46 (23.5)	51 (18.0)	60 (21.4)	157 (20.7)
Levetiracetam	45 (15.6)	23 (11.7)	39 (13.7)	44 (15.7)	106 (13.9)
Topiramate	37 (12.8)	21 (10.7)	43 (15.1)	41 (14.6)	105 (13.8)
Phenytoin	26 (9.0)	15 (7.7)	35 (12.3)	28 (10.0)	78 (10.3)
Phenobarbital	34 (11.8)	15 (7.7)	32 (11.3)	25 (8.9)	72 (9.5)
Clobazam	24 (8.3)	19 (9.7)	27 (9.5)	18 (6.4)	64 (8.4)
Clonazepam	15 (5.2)	19 (9.7)	20 (7.0)	16 (5.7)	56 (7.4)
Gabapentin	3 (1.0)	12 (6.1)	8 (2.8)	8 (2.9)	28 (3.7)
Primidone	4 (1.4)	2 (1.0)	6 (2.1)	7 (2.5)	15 (2.0)
Tiagabine	1 (0.3)	2 (1.0)	2 (0.7)	7 (2.5)	11 (1.4)
Pregabalin	2 (0.7)	1 (0.5)	3 (1.1)	6 (2.1)	10 (1.3)

In the 400 mg dose group, valproic acid was given as concomitant AED in only 18.9 % of subjects compared to 28.4 % in the placebo group.

In study 302 valproic acid was only used by 12.5% of patients in the 400 mg dose group compared to 26.0% in the placebo group, whereas it was used by 28.0% of patients in the 800 mg and by 20.6% of patients in the 1200 mg dose group, respectively.
However, in the subgroup analysis of the integrated phase III studies the trend in the median relative reduction was similar in subjects not taking valproic acid (placebo: -10.1%, 400 mg: -23.0%, 800 mg: -33.3%, 1200 mg: -38.3%) and those taking valproic acid (placebo: -26.4%, 400 mg: -26.8%, 800 mg: -41.8%, 1200 mg: -39.9%).
The ANCOVA results for the standardised seizure frequency and relative reduction in seizure frequency by concomitant valproic acid treatment showed comparable efficacy of Exalief during the maintenance phase in the different dose groups compared to placebo in patients taking valproic acid compared to patients taking no valproic acid.
The responder rate was similar in subjects not taking valproic acid (placebo: 18.8%, 400 mg: 22.4%, 800 mg: 34.0%, 1200 mg: 44.6%) and those taking valproic acid (placebo: 28.6%, 400 mg: 25.0%, 800 mg: 42.6%, 1200 mg: 40.3%.
Therefore, the described imbalances do not appear to have influenced the efficacy results.

During the titration and maintenance periods, 38.1% of placebo and 52.2% of total Exalief subjects took concomitant non-AED medications, with a similar proportion in each of the Exalief groups.

During the study, 54.0% of placebo subjects and 56.2% of total Exalief subjects had concomitant medical conditions (other than epilepsy).

In the different Exalief dose groups and the placebo group there were no major differences regarding the number of concomitant AEDs per patient at baseline. The majority of patients of all groups used two concomitant AEDs, the proportion of these patients ranging from 59.6% (in the Exalief 400 mg group) to 68.4% (in the Exalief 800 mg group).
The most frequently administered concomitant anti-epileptic medications at baseline were carbamazepine (taken by 55.6 – 61.8% of the ITT patients, depending on the treatment group), lamotrigine (24.2 – 27.6%) and valproic acid (22.4% - 28.4%).
Furthermore, subgroup-analyses of the integrated phase III studies did not reveal any influence of these parameters on the efficacy of Exalief in each dose group.

- Outcomes and estimation

Standardised seizure frequency:
For the natural log transformation of the seizure frequency per 4 weeks over the 12-week maintenance period, which was the primary efficacy variable in all 3 pivotal studies, a statistically significant difference was seen for the comparison of the 800 mg and 1200 mg groups compared to placebo in every single of the 3 studies:

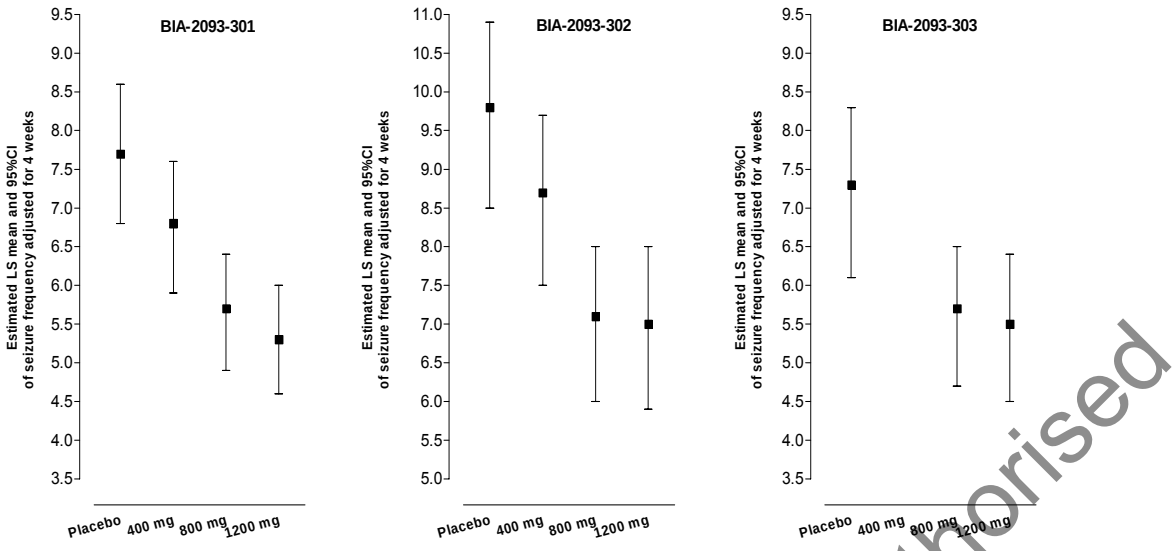
Table: Primary Efficacy Analysis - ANCOVA for seizure frequency per 4 weeks over the 12-week maintenance period (ITT population)

Study	LS Mean [95%CI] p-value[a]			
	Placebo	**ESL 400 mg**	**ESL 800 mg**	**ESL 1200 mg**
BIA-2093-301	7.6 [6.8, 8.6]	6.7 [6.0, 7.7] n.s.	5.7 [5.0, 6.5] p=0.003	5.4 [4.6, 6.1] p < 0.001
BIA-2093-302	9.8 [8.7, 11.1]	8.7 [7.7, 9.9] n.s.	7.1 [6.2, 8.2] p=0.002	7.0 [6.0, 8.1] p=0.001
BIA-2093-303	7.3 [6.3, 8.5]	N/A	5.7 [4.9, 6.7] p=0.048	5.5 [4.6, 6.5] p=0.021

ITT = intent-to-treat; LS = least square; N/A = not applicable; n.s. = not significant
a p-value for comparison to placebo.

As it can be seen in the following figure, the LS mean of seizure frequency decreased in a dose-dependent manner in all of the single studies, however, the increase in effect in study 302 after administration of 1200 mg compared to 800 mg was only small.

Figure: Seizure frequency per 4 weeks over the 12-week maintenance period - individual Phase III studies (ITT population)



Source data: Table EF.2.1 and Table EF.2.2 in Study Report INT/PhaseIII/301-303

In the integrated dataset of the ITT population, the median standardised seizure frequency at baseline was similar in all treatment groups (range: 7.0 to 8.0). During the 12-week maintenance period the median standardised seizure frequency was lowest in the 1200 mg Exalief group (4.6) and highest in the placebo group (6.4):

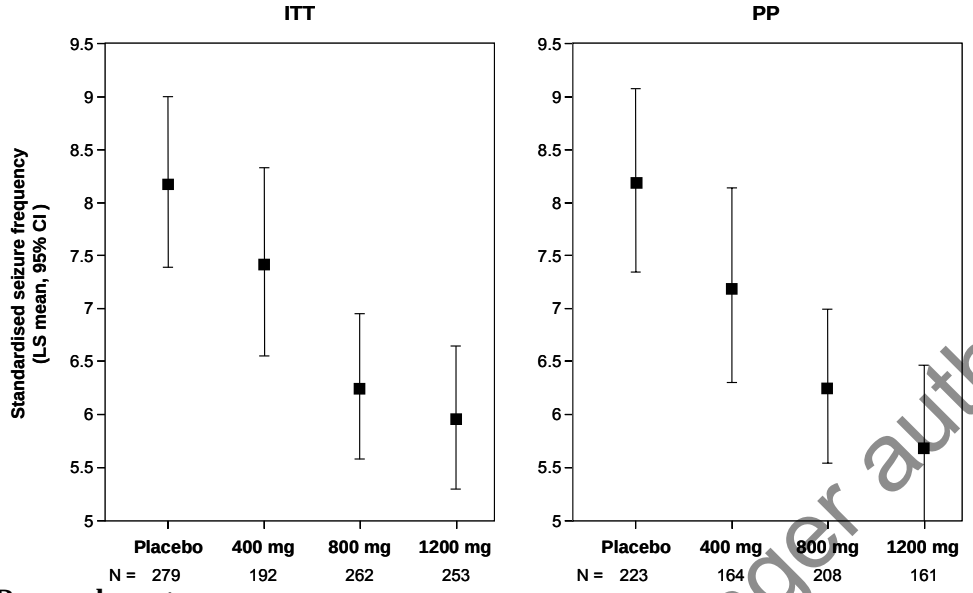
Standardised seizure frequency - Phase III integrated studies (ITT population)

Study/	Baseline Period			Maintenance Period		
Treatment	**N**	**Mean±SD**	**Median**	**N**	**Mean±SD**	**Median**
Integrated Studies						
Placebo	286	12.9±16.82	7.0	279	11.7±17.85	6.4
ESL 400 mg	195	13.0±15.08	8.0	192	10.6±13.11	5.9
ESL 800 mg	282	13.4±15.31	7.7	262	9.8±14.79	5.0
ESL 1200 mg	272	13.3±15.26	8.0	253	9.0±13.10	4.6

The ANCOVA analysis of the integrated data from all 3 studies showed that compared to the placebo group the change in standardised seizure frequency during the maintenance period was statistically significant ($p<0.0001$) for the 800 mg and 1200 mg Exalief groups in the ITT and PP populations. In the PP population, the difference between the 400 mg and placebo group was also statistically significant ($p=0.0369$).

The dose related increase in effect is shown in the following figures:

Figure: Standardised seizure frequency - Phase III integrated studies (ITT and PP populations)



Responder rate

The responder rate (subjects with a change in standardised seizure frequency ≥50% relative to baseline) was considerably higher in the Exalief 800 mg and 1200 mg groups than in the placebo group in each of the 3 studies as well as in the integrated analysis of the 3 studies in the ITT population and increased with increasing dose.

The difference to placebo was statistically significant for the 800 mg and 1200 mg Exalief groups in study 301 and 302 and in the integrated analyses of the 3 studies in the ITT population. In study 303, the difference to placebo was only statistically significant for the 1200 mg but not for the 800 mg dose group (in both, the ITT and PP populations). For the 400 mg dose group, the difference to placebo was not statistically significant in any of the single studies or the integrated analysis of all 3 studies.

Table: Responder analysis - Phase III integrated studies (ITT population)

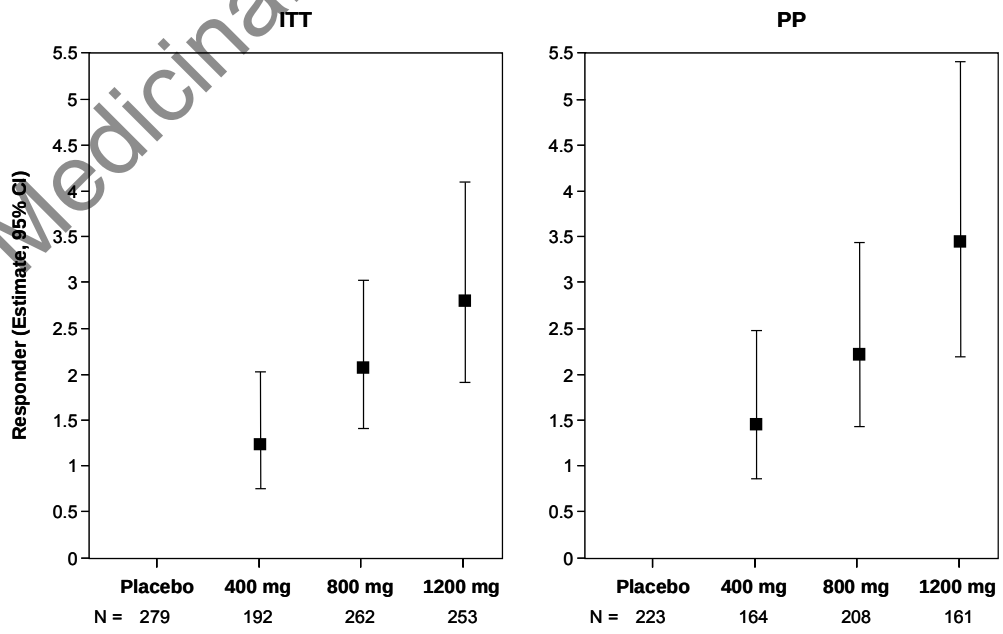
Study/ Treatment	N	Number (%) of responders	Odds ratio		Relative Risk		Overall p-value
			Estimate	95% CI	Estimate	95% CI	
301							
Placebo	99	20 (20.2)	-	-	-	-	-
ESL 400 mg	97	23 (23.7)	1.23	(0.62, 2.42)	1.17	(0.69, 1.99)	0.5528
ESL 800 mg	94	33 (35.1)	2.14	(1.12, 4.09)	1.74	(1.08, 2.80)	0.0204
ESL 1200 mg	94	42 (44.7)	3.19	(1.69, 6.03)	2.21	(1.41, 3.47)	0.0003
302							

Study/ Treatment	N	Number (%) of responders	Odds ratio Estimate	Odds ratio 95% CI	Relative Risk Estimate	Relative Risk 95% CI	Overall p-value
Placebo	99	18 (18.2)	-	-	-	-	-
ESL 400 mg	95	21 (22.1)	1.28	(0.63, 2.58)	1.22	(0.69, 2.14)	0.4955
ESL 800 mg	88	33 (37.5)	2.70	(1.38, 5.27)	2.06	(1.25, 3.39)	0.0031
ESL 1200 mg	86	36 (41.9)	3.24	(1.66, 6.31)	2.30	(1.42, 3.74)	0.0004
303							
Placebo	81	22 (27.2)	-	-	-	-	-
ESL 400 mg	-	-	-	-	-	-	-
ESL 800 mg	80	29 (36.3)	1.52	(0.78, 2.98)	1.33	(0.84, 2.11)	0.2151
ESL 1200 mg	73	32 (43.8)	2.09	(1.07, 4.10)	1.61	(1.04, 2.51)	0.0304
Integrated Studies							
Placebo	279	60 (21.5)	-	-	-	-	-
ESL 400 mg	192	44 (22.9)	1.25	(0.77, 2.04)	1.19	(0.81, 1.76)	0.3668
ESL 800 mg	262	95 (36.3)	2.08	(1.42, 3.04)	1.69	(1.28, 2.22)	0.0001
ESL 1200 mg	253	110 (43.5)	2.81	(1.92, 4.10)	2.02	(1.55, 2.63)	<0.0001

ITT = intent-to-treat; CI = confidence interval; Responder: relative change in standardised seizure frequency ≥50% in comparison to baseline period.

The dose related increase in responder rate is shown in the following figures:

Figure: Responder analysis - Phase III integrated studies (odds ratio - ITT and PP populations)



The CHMP considered that the results of the responder analyses of the three single studies as well as of the integrated analysis of the 3 studies were considered consistent: the responder rate increased in a dose dependent way and (in contrast to the 400 mg dose group) the difference to placebo was statistically significant for the 800 and 1200 mg dose groups, except in study 303, in which the difference to placebo was only statistically significant for the 1200 mg dose group.

The formal assessment of the differences concerning responder rate in study 303, the relative reduction in seizure frequency in study 302 and the change in median number of days with seizures in study 302 compared to the results of the respective other studies was further discussed in the answer to the List of questions, and did not reveal significant heterogeneities between the pivotal studies.

Apparently, in the three single studies as well as in the integrated analysis patients who discontinued treatment prematurely during one of the treatment periods were still categorized as treatment responders for that particular treatment period when their seizure frequency was reduced by 50% or more up to the point of discontinuation. The applicant was asked to provide a supplementary responder analysis for all three main trials as well as the integrated analysis in which all patients who discontinued are regarded as non-responders.
The results of this supplementary responder analysis, in which discontinued subjects were analysed as non-responders, were consistent with those of the original analysis and confirm the improved responder rate with 800 mg and 1200 mg Exalief QD compared to placebo.

Relative reduction of standardised seizure frequency
The relative reduction in standardised seizure frequency during the maintenance period was greater in the Exalief treatment groups than in the placebo group in all 3 studies and the integrated analysis in the ITT population. In the integrated studies, the median relative change was -14.6% in the placebo group compared to -23.4% in the 400 mg Exalief group, -35.4% in the 800 mg Exalief group, and -38.8% in the 1200 mg Exalief group.

Table: Relative reduction (%) of standardised seizure frequency - Phase III integrated studies (ITT population)

Study/ Treatment	N	Mean±SD	Median	Range
301				
Placebo	99	-8.0±58.95	-16.4	-100 to 289
ESL 400 mg	97	-16.4±81.56	-25.8	-100 to 685
ESL 800 mg	94	-31.0±43.58	-36.1	-100 to 147
ESL 1200 mg	94	-35.4±46.85	-46.5	-100 to 81
302				
Placebo	99	1.6±61.75	-5.8	-100 to 316
ESL 400 mg	95	-13.7±48.73	-22.4	-100 to 154
ESL 800 mg	88	-25.9±58.90	-33.8	-100 to 286
ESL 1200 mg	86	-22.5±67.74	-32.3	-100 to 328
303				
Placebo	80	-8.2±69.73	-20.8	-100 to 308
ESL 400 mg	-	-	-	-
ESL 800 mg	80	-19.9±72.02	-36.4	-100 to 384

Study/ Treatment	N	Mean±SD	Median	Range
ESL 1200 mg	71	-21.8±105.20	-43.1	-100 to 716
Integrated Studies				
Placebo	278	-4.6±63.14	-14.6	-100 to 316
ESL 400 mg	192	-15.0±67.19	-23.4	-100 to 685
ESL 800 mg	262	-25.9±58.51	-35.4	-100 to 384
ESL 1200 mg	251	-27.1±74.27	-38.8	-100 to 716

ITT = intent-to-treat; SD = standard deviation.

The ANCOVA of the integrated data from all 3 studies showed that the difference in the relative reduction in standardised seizure frequency was statistically significant between the placebo group and the 800 mg and the 1200 mg groups in the ITT and PP populations.

Responder rate and relative reduction in standardised seizure frequency per week

In the phase III integrated studies, the response to treatment was evident already in the first week of the titration period and had reached its peak in the first week of the maintenance period. The responder rate was approximately 46% of subjects in the Exalief 800 mg group and 50% in the Exalief 1200 mg group in the first week of the maintenance period, and remained stable through the last week of the maintenance period (week 12).

The standardised seizure frequency also decreased already during the titration period and continued to decrease until reaching a steady state by week 4 of the maintenance period.

Seizure type
In the phase III integrated studies, the standardised seizure frequency by seizure type showed a difference compared to placebo for simple partial and for complex partial seizures.

Table: Standardised seizure frequency by seizure type - Phase III integrated studies (ITT population)

Seizure Type/ Treatment	Baseline Period				Maintenance Period			
	N	n	Mean±SD	Median	N	n	Mean±SD	Median
Simple Partial								
Placebo	286	137	4.9±11.25	0	279	142	4.7±12.88	0.3
ESL 400 mg	195	86	5.1±13.13	0	192	88	4.8±12.24	0
ESL 800 mg	282	136	5.6±11.67	0	262	118	3.9±12.15	0
ESL 1200 mg	272	130	4.9±10.14	0	253	109	3.4±7.85	0
Complex Partial								
Placebo	286	197	5.7±12.19	3.4	279	192	5.4±11.27	2.0
ESL 400 mg	195	139	5.8±7.99	3.9	192	135	4.5±6.87	2.3
ESL 800 mg	282	207	6.2±9.67	3.8	262	178	4.4±6.94	2.0
ESL 1200 mg	272	200	6.1±11.89	3.8	253	154	4.3±11.17	1.0
Partial evolving to secondarily generalised								
Placebo	286	92	1.3±3.88	0	279	85	0.9±2.44	0
ESL 400 mg	195	66	1.3±3.48	0	192	52	0.9±2.34	0
ESL 800 mg	282	84	1.1±3.00	0	262	72	0.8±2.51	0
ESL 1200 mg	272	88	1.2±3.47	0	253	68	0.7±2.08	0
Unclassified								
Placebo	286	44	1.0±4.55	0	279	51	0.7±3.34	0
ESL 400 mg	195	21	0.8±4.95	0	192	24	0.4±1.74	0
ESL 800 mg	282	44	0.6±2.96	0	262	44	0.6±4.05	0
ESL 1200 mg	272	41	1.1±4.35	0	253	40	0.6±2.30	0

ITT = intent-to-treat; n = number of subjects with seizures of the respective type; N = total number of subjects with available data; SD = standard deviation.

Concerning the 2 other seizure types (partial evolving to secondarily generalised and unclassified seizures) the number of subjects and seizure frequency was low and no meaningful interpretation can be made of these data.

With respect to secondarily generalised seizures, the following is found, when the 3 pivotal studies are looked at separately (ITT population):

Study 301:

Compared to the respective baseline level marked reductions of seizure frequency during the 12-week maintenance period were found for the mean number of partial evolving to secondarily generalised seizures in the Exalief 800 mg group (from 4.1 to 2.7).
Decreases of medians regarding the number of partial evolving to secondarily generalised seizures in the Exalief 800 mg group (from 2.5 to 0.9) exceeded corresponding changes observed in the placebo group (ITT population).
However, for the 1200 mg dose group, the reduction in median seizure frequency compared to the respective baseline level appears to be smaller than in the placebo group.

Study 302:

The relative reduction in median standardised seizure frequency was higher in the 1200 mg dose group compared to the placebo group, however a higher efficacy for the 800 mg and 1200 mg dose groups compared to placebo and a dose related trend could only be seen, when data from titration period where included.

From Study 303 no trend concerning efficacy of Exalief for the treatment of secondary generalised seizures can be derived.

As the CHMP considered that no clear trend towards efficacy of Exalief in the treatment of secondary generalised seizures was seen, further analysis of the data was requested.
An ANCOVA for the standardised seizure frequency during the maintenance period was performed to compare treatments for subjects with partial evolving to secondarily generalized seizures at baseline using the following model:
ln(stand seizure freq + 4) = treatment + ln(baseline value+4) + Number of concomitant AEDs at baseline + error.
The results of the ANCOVA clearly demonstrate the efficacy of the 800 mg Exalief and the 1200 mg Exalief treatment groups in comparison to placebo for the ITT population [Table EF.2.1.8 in Study INT/Phase III/301-303]:
p=0.0001 for testing the hypothesis H0: 1200 mg Exalief – placebo=0
p=0.0147 for testing the hypothesis H0: 800 mg Exalief – placebo=0

To address this point, also a responder analysis (relative change in seizure frequency ≥50% in comparison to baseline period) was calculated for subjects with partial evolving to secondarily generalized seizures at baseline. The overall p-values from the CMH test (stratified by study) and from the Chi-square test did not show any statistical significance nor did the p-values from the pairwise tests of Exalief groups versus placebo. However, only about 30% of subjects from the 3 Phase III studies had partial evolving to secondarily generalized seizures at baseline, and thus the power of these responder analyses was not sufficient to show any significant differences between treatment groups.
What could be seen is that the trend in this subgroup was the same as for the overall population. The proportion of responders in each treatment group increased from 19.8% in the placebo group to 21.2% in the 400 mg Exalief group, 37.5% in the 800 mg Exalief group and 47.1% in the 1200 mg Exalief group.

The CHMP considered that though the number of patients with secondary generalized seizures was low in the pivotal studies, both the ANCOVA results for the standardised frequency of secondary generalized seizures during maintenance phase and the clear trend seen in the responder analysis (which was generally the same than for partial seizures overall though not statistically significant) are strongly indicative of efficacy of Exalief in the treatment of secondary generalized seizures. Taken into consideration, that secondary generalized seizures evolve from primary partial seizures, for which efficacy of Exalief has been shown, the response is considered sufficient and supports the use of Exalief in these subjects.

The ANCOVA of standardised seizure frequency by seizure type showed that the difference compared to placebo for simple partial and complex partial seizures was statistically significant for the 800 mg and 1200 mg groups.

Table: ANCOVA analysis of standardised seizure frequency by seizure type - Phase III integrated studies (ITT population)

Treatment	N	LS Mean	SE	95% CI	p-value	
					Pairwise Comparison to Placebo	Overall Treatment Effect
Simple partial						
Placebo	279	2.35	0.021	(2.09, 2.61)	-	0.0004
ESL 400 mg	192	2.23	0.025	(1.93, 2.54)	0.5656	
ESL 800 mg	262	1.71	0.022	(1.47, 1.95)	0.0004	
ESL 1200 mg	253	1.76	0.022	(1.63, 2.01)	0.0014	
Complex partial						
Placebo	279	3.34	0.023	(3.02, 3.68)	-	0.0001
ESL 400 mg	192	2.95	0.028	(2.59, 3.34)	0.1276	
ESL 800 mg	262	2.68	0.024	(2.38, 2.99)	0.0039	
ESL 1200 mg	253	2.30	0.024	(2.01, 2.60)	<0.0001	

CI = confidence interval; ITT = intent-to-treat; LS = least square; N = total number of subjects; SE = standard error.

Note: The ANCOVA model was based on log-transformed seizure frequencies with treatment, study, baseline seizure frequency and number of concomitant AEDs at baseline as factors. Least square means and confidence limits for the absolute effects within treatment groups have been back-transformed via the exponential function. Dunnetts multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

Concerning standardised seizure frequency, the effect was somewhat pronounced in the 800 mg dose group compared to the 1200 mg for simple partial seizures, and a clear dose-related effect was seen for complex partial seizures.

A responder analysis by seizure type showed that subjects treated with Exalief 800 mg and 1200 mg had a greater response than placebo for simple partial and complex partial seizures, and the percentage of responders was higher in the 1200 mg dose group than in the 800 mg dose group for both seizure types.

Table: Responder analysis by seizure type - Phase III integrated studies (ITT population)

Seizure Type/ Treatment	N	Number (%) responders	Odds ratio		Relative Risk		Overall p-value
			Estimate	95% CI	Estimate	95% CI	
Simple Partial							
Placebo	133	39 (29.3)	-	-	-	-	-
ESL 400 mg	84	26 (31.0)	1.41	(0.72, 2.74)	1.28	(0.79, 2.08)	0.3155
ESL 800 mg	127	61 (48.0)	2.23	(1.34, 3.71)	1.64	(1.19, 2.26)	0.0019
ESL 1200 mg	123	63 (51.2)	2.53	(1.51, 4.23)	1.75	(1.27, 2.39)	0.0003
Complex Partial							
Placebo	191	59 (30.9)	-	-	-	-	-
ESL 400 mg	137	39 (28.5)	0.99	(0.59, 1.66)	0.99	(0.69, 1.44)	0.9698
ESL 800 mg	193	83 (43.0)	1.69	(1.11, 2.57)	1.39	(1.07, 1.82)	0.0139
ESL 1200 mg	188	100 (53.2)	2.54	(1.67, 3.87)	1.72	(1.34, 2.21)	<0.0001

CI = confidence interval; ITT = intent-to-treat; N = number of subjects who had the seizure type during the baseline period and with available data during the maintenance period; Responder: relative change in standardised seizure frequency ≥50% in comparison to baseline period.

Efficacy analyses concerning simple partial and complex partial seizures demonstrate a relevant effect of the 800 mg and 1200 mg dose on both seizure types. Responder analysis revealed a dose response for both seizure types and analysis of standardised seizure frequency showed a clear dose related effect for complex partial seizures.

Categorised relative change in standardised seizure frequency

In the phase III integrated studies, the relative reduction in standardised seizure frequency increased with increasing dose of Exalief during the maintenance period.

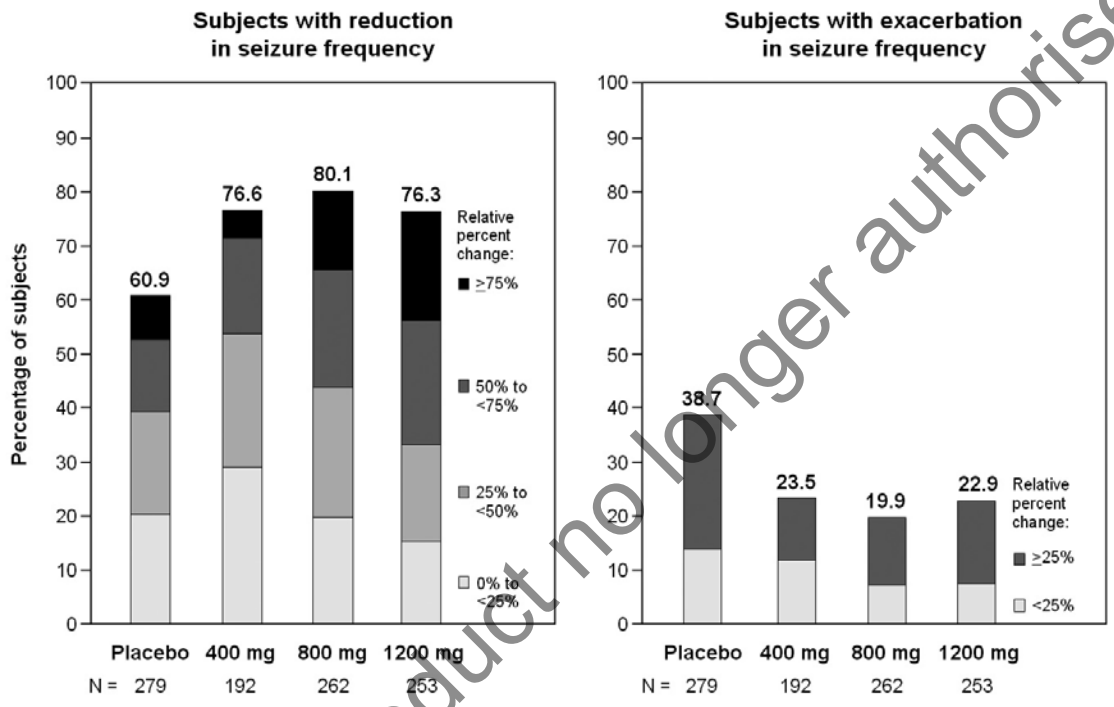
Table: Relative (%) change in standardised seizure frequency during the maintenance period compared to baseline - Phase III integrated studies (ITT population)

Treatment	N	Reduction				Exacerbation		Missing
		≥75%	50% to <75%	25% to <50%	0% to <25%	<25%	≥25%	
Placebo	279	8.2	13.3	19.0	20.4	14.0	24.7	0.4
ESL 400 mg	192	5.2	17.7	24.5	29.2	12.0	11.5	0
ESL 800 mg	262	14.5	21.8	24.0	19.8	7.3	12.6	0
ESL 1200 mg	253	20.2	22.9	17.8	15.4	7.5	15.4	0.8

ITT = intent-to-treat.

A larger proportion of Exalief subjects (60.3% of 800 mg subjects and 60.9% of 1200 mg subjects) had a reduction in standardised seizure frequency of 25% or more compared to placebo subjects (40.5%). While 38.7% of placebo subjects had an exacerbation of seizure frequency, less than 24% of subjects in any Exalief group did so. However the percentage of patients with an increase in seizure frequency, especially with an increase of ≥ 25% is slightly higher in the 1200 mg dose group compared to the 800 mg dose group (see next figure).

Figure: Relative (%) change in standardised seizure frequency during the maintenance period compared to baseline - Phase III integrated studies (ITT population)



Concerning exacerbation of seizures, the same trend concerning the verum groups was seen, when study 301 was analysed solely:
The proportion of patients with a 25% or greater exacerbation in seizure frequency during maintenance phase versus baseline was highest in the placebo group (21.6%); in the verum groups however, it was lowest in the 400 mg dose group (8.1%) and highest in the 1200 mg dose group (12.2%).

In study 302 the proportion of patients with a 25% or greater exacerbation in seizure frequency during maintenance phase versus baseline was highest in the placebo group (28.0%); in the verum groups it was lowest in the 800 mg dose group (10.0%), intermediate in the 1200 mg dose group (14.4%) and highest in the 400 mg dose group (15.6%).

In study 303, however, the proportion of patients with a 25% or greater exacerbation in seizure frequency during maintenance phase versus baseline was lowest in the 1200 mg dose group (13.0%), compared to the 800 mg dose group (16.7%) and the placebo group (22.6%), respectively.

The CHMP noted that in the integrated phase III analysis, the percentage of subjects with a ≥50% relative reduction in standardised seizure frequency is higher in the 800 mg and 1200 mg dose groups compared to placebo, and especially for the ≥75% relative reduction the effect is larger in the 1200 mg dose group compared to the 800 mg dose group.

The percentage of patients with an exacerbation in seizure frequency during the maintenance phase compared to the baseline is clearly higher in the placebo group compared to each of the treatment groups. However the percentage of patients with an increase in seizure frequency, especially with an increase of ≥ 25% is slightly higher in the 1200 mg dose group compared to the 800 mg dose group in the integrated phase III analysis and in studies 301 and 302, respectively.

The applicant was requested to further evaluate and discuss the potential of Exalief to induce seizures and to worsen specific seizure types. For this purpose, increase in seizure frequency < 25% and ≥ 25%, respectively should be presented for different seizure types (including absences) for the individual studies as well as the integrated analysis.

Exacerbations in seizure frequency during Maintenance Period (Overall and by Seizure Type)

Seizure type	% Exacerbation	Number (%) of subjects			
		Placebo	ESL		
		(N=279)	400 mg (N=192)	800 mg (N=262)	1200 mg (N=253)
Overall	<25%	39 (14.0)	23 (12.0)	19 (7.3)	19 (7.5)
	≥25%	69 (24.7)	22 (11.5)	33 (12.6)	39 (15.4)
Simple partial	<25%	16 (5.7)	10 (5.2)	4 (1.5)	11 (4.3)
	≥25%	39 (14.0)	16 (8.3)	21 (8.0)	20 (7.9)
Complex partial	<25%	25 (9.0)	16 (8.3)	13 (5.0)	10 (4.0)
	≥25%	47 (16.8)	15 (7.8)	30 (11.5)	26 (10.3)
Partial evolving to secondarily generalised	<25%	5 (1.8)	7 (3.6)	5 (1.9)	4 (1.6)
	≥25%	11 (3.9)	10 (5.2)	11 (4.2)	12 (4.7)
Unclassified	<25%	0	2 (1.0)	2 (0.8)	0
	≥25%	6 (2.2)	2 (1.0)	3 (1.1)	6 (2.4)

Source: (Table Q48-1 and Q48-2 in Appendix 35)

The percentage of patients experiencing absence seizures during baseline and/or maintenance phase was very low (placebo group: 0.4% of patients during baseline, 0.7% during maintenance; 400 mg dose group: 0.5% during baseline, 0% during maintenance; 800 mg dose group: 0.4% during baseline, 1.1% during maintenance; 1200 mg dose group: 1.2% during baseline, 1.6% during maintenance). The frequency of patients experiencing absences are too low to draw definite conclusions, however, from the data presented there is no clear indication of a potential of Exalief to increase absences.
It was concluded that there is no indication for a potential exacerbation of seizures during treatment with Exalief.

Number of days with seizures:
In the integrated phase III analysis, the median standardised number of days with seizures per 4 weeks was between 5.9 and 6.5 in all treatment groups at baseline. The standardised number of days already decreased during the titration period in the Exalief 800 mg (p=0.0018) and 1200 mg groups (p=0.0249). During the maintenance period the median standardised number of days with seizures per 4 weeks was 5.3 in the placebo group compared to 4.3 in the 800 mg Exalief group (p=0.0054) and to 3.8 in the 1200 mg group (p=0.0007).

Table: Standardised number of days with seizure per 4 weeks - Phase III integrated studies (ITT population)

Treatment	Baseline Period			Maintenance Period			
	N	Mean±SD	Median	N	Mean±SD	Median	p-value
Placebo	286	8.0±5.70	5.9	279	7.0±5.83	5.3	-
ESL 400 mg	195	8.5±5.58	6.5	192	7.0±5.83	5.1	0.4410
ESL 800 mg	282	8.5±5.81	6.5	262	6.1±5.77	4.3	0.0054
ESL 1200 mg	272	8.6±6.17	6.3	253	6.1±6.22	3.8	0.0007

ITT = intent-to-treat; N = total number of subjects with available data; SD = standard deviation.

Note: p-values generated with a Cochran-Mantel-Haenszel test using modified ridit scores with study as stratification factor.

In study 302, the Exalief 800 mg group (ITT population) had the greatest differences in median number of days with seizures between the baseline period value and the 12-week maintenance period value (3.2) and the 2-week titration + 12-week maintenance periods value (3.0). Differences in median values in the Exalief 1200 mg group were 1.8 and 1.6, respectively.

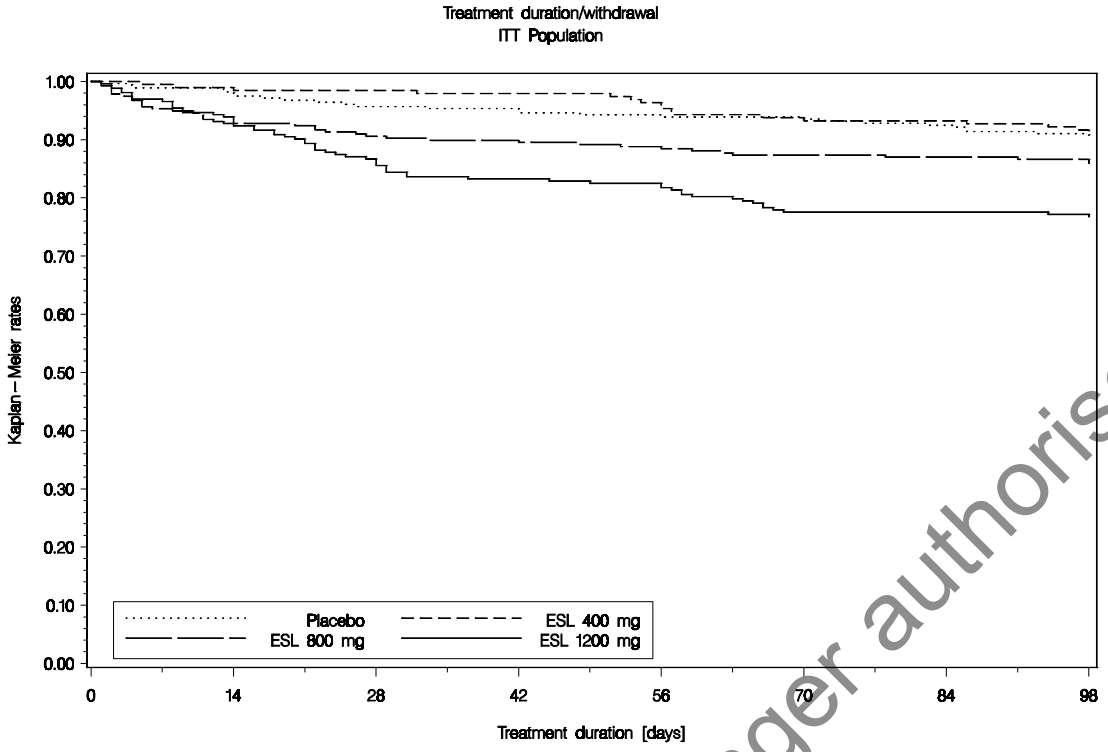
Seizure-free subjects

In the integrated phase III analysis, the proportion of subjects who were seizure-free during the maintenance period increased with increasing dose of Exalief, from 2% to 3% of subjects in the placebo and Exalief 400 mg groups to 3.8% of subjects in the 800 mg group and 8% of subjects in the 1200 mg group.

Treatment retention time

In the integrated phase III analysis, treatment retention time was similar in the placebo and 400 mg groups and decreased with higher doses of Exalief. Findings in the safety population were the same as for the ITT population and were generally the same in the three single studies. Most discontinuations were because of unacceptable AEs which occurred in a treatment- and dose-dependent manner.

Figure: Treatment retention time - Phase III integrated studies (ITT population)



Note: The plot is restricted to 98 days, which is the planned duration of titration and maintenance period in all studies.

Efficacy during tapering period

During the tapering-off period (studies 301 and 303 only), the standardised seizure frequency remained essentially constant in the placebo group relative to the end of the maintenance period and increased slightly in the Exalief groups without any sign of a rebound effect.

Table: Standardised seizure frequency in tapering-off period - Studies BIA-2093-301 and BIA-2093-303 (ITT population)

Treatment Group	Study BIA-2093-301			Study BIA-2093-303		
	N	Mean±SD	Median	N	Mean±SD	Median
Baseline Period						
Placebo	102	12.4±17.94	6.7	84	12.9±18.31	6.5
ESL 400 mg	99	11.4±9.74	7.5	-	-	-
ESL 800 mg	98	11.2±11.21	7.0	84	13.1±18.58	7.8
ESL 1200 mg	98	11.6± 15.92	7.5	77	12.1±12.83	6.0
Maintenance Period						
Placebo	99	11.1±17.21	6.7	81	11.2±21.62	5.7
ESL 400 mg	97	8.9±9.51	5.7	-	-	-
ESL 800 mg	94	7.1±8.11	4.8	80	9.7±14.42	4.6
ESL 1200 mg	94	8.1±15.51	4.7	73	7.8±10.45	3.7
Tapering-off Period						
Placebo	88	9.1±15.85	5.8	70	10.3±19.70	5.4
ESL 400 mg	93	9.1±11.66	5.0	-	-	-
ESL 800 mg	85	8.2±9.04	5.8	73	10.0±12.92	5.4
ESL 1200 mg	73	9.5±18.45	5.8	60	8.0±8.17	5.1

ITT = intent-to-treat; N=total number of subjects; SD = standard deviation.

Interaction between doses of Exalief and concomitant anti-epileptic drugs

In the integrated phase III analysis, based on the ANCOVA model, no effect was seen on the efficacy of Exalief when given concomitantly with carbamazepine, lamotrigine, or valproic acid.

Health related questionnaires

Clinical global impression (CGI)
On the Global Improvement scale, a larger percentage of Exalief subjects than placebo subjects had been noted at the end of the maintenance period (V5) as much improved (21.2% placebo, 29.4% Total Exalief) or very much improved (5.4% placebo, 10.4% Total Exalief), and this effect was greatest in the 800 mg and 1200 mg Exalief groups. Similar results were seen for therapeutic effect.
At the end of the maintenance period side effects were reported by 24.2% of placebo subjects and 27.6% of Exalief subjects, and ≤ 5% of subjects considered these to significantly interfere with their functioning.

Motgomery &Asberg depression rating scale (MADRS)
Symptoms of depression as assessed by the MADRS did not show major changes from the randomisation visit to the last visit in either the placebo or Exalief groups.

Quality of life in epilepsy inventory-31 (Quolie-31)
There were no major changes of QOLIE-31 mean scores from randomisation to the last visit for any of the subscales or on the overall score in either the placebo or Exalief groups.

Study 303:
Whereas in studies 301 and 302 major protocol violations where at an acceptable level (in study 301 only 4 Patients were excluded from PP population because of major protocol violations, in study 302 major protocol violations occurred in 14.4% of patients) the percentage of patients with major protocol violations in study 303 was remarkable (33.6%):

Table 10-1. Major Protocol Violations Affecting > 5 Patients Overall (ITT Population)

	Placebo (N=84) n (%)	ESL 800 mg (N=84) n (%)	ESL 1200 mg (N=77) n (%)	Total (N=245) n (%)
Any Protocol Violation	26 (31.0)	30 (35.7)	29 (37.7)	85 (34.7)
Baseline period was only two weeks.	5 (6.0)	6 (7.1)	7 (9.1)	18 (7.4)
Baseline seizure frequency per 4 weeks is less than 4.	13 (15.5)	13 (15.5)	13 (16.9)	39 (15.9)
Blinded codes broken at completion of double-blind assessment period.	1 (1.2)	2 (2.4)	2 (2.6)	5 (2.0)
Non-compliance with dosage regimen.	2 (2.4)	3 (3.6)	0 (0.0)	5 (2.0)
Study drug compliance during the double-blind assessment period ≤ 80% or > 120%	8 (9.5)	6 (7.1)	9 (11.7)	23 (9.4)

Cross reference: Table 14.1-1.7.2.

The blind was broken for 5 patients immediately after study completion. To assess the potential impact this deviation had on results from this study, a restricted ITT population, in which data for these 5 patients were removed from the ITT population, was used for several efficacy analyses:

In contrast to the results from ANCOVA analysis of seizure frequency per 4 weeks over the 12-week maintenance period in the complete ITT population (which had shown a statistically significant and dose dependent effect of the Exalief 800 mg and 1200 mg groups), ANCOVA analysis of the restricted ITT population revealed no statistically significant difference between the Exalief 800 mg and the placebo groups.

However, results were almost the same between the complete and restricted ITT populations for median absolute and relative reductions in seizure frequency or the proportions of responders, seizure-free patients and patients with a ≥ 25% exacerbation in seizure frequency over the 12-week maintenance period.

Furthermore, in the PP population, ANCOVA analysis for seizure frequency per 4 weeks over the 12-week maintenance period (as well as the 2-week titration + 12 week maintenance periods) revealed no statistically significant difference between treatment and placebo groups, which might be due to a low sample size for the PP population compared with that of the ITT population (133 vs. 245 patients, respectively). The LS mean difference to placebo was greater in the Exalief 1200 mg group than in the Exalief 800 mg group (-1.6 versus -1.2, respectively).

As has been shown above the responder rates for the 800 and 1200 mg dose groups clearly exceeded that of the placebo group, but the difference compared to placebo was statistically significant only for the 1200 mg dose group.
Additionally, some inconsistencies in the analyses of the accessory secondary efficacy parameters were found.

The CHMP was concerned by the frequency and character of the major protocol violations of study 303, raising doubts on the reliability of the study results. Whereas the results of studies 301 and 302 were highly consistent, some results of study 303 were considered implausible. The applicant was therefore requested to repeat the integrated analysis without study 303: the analysis with excluded study 303 was not significantly different from the overall integrated analysis. Although the drop-out rate in the study 303 was relatively high, the overall results did not change after excluding this study from the analysis.

- Ancillary analyses

Analysis of subpopulations
In the integrated phase III analysis, the trend for increasing efficacy with increasing dose of Exalief was generally consistent among sub-populations. No relevant difference was found between men and women, geographical regions, subjects with longer (≥20 years) or shorter (<20 years) epileptic duration, for subjects <18 years at diagnosis or between 18 and 50 years, for number of concomitant AEDs (1 or 2). While the same dose-dependent trend was seen for Hispanics, it was less pronounced than for Caucasians.

The efficacy seen in each dose group was generally comparable during the maintenance period regardless of whether subjects were taking concomitant carbamazepine, lamotrigine or valproic acid.

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

The integrated analysis of the 3 pivotal studies has already been described above (Main studies).

Clinical studies in special populations

Children

One open-label phase II study in children with epilepsy has been performed BIA-2093-202, and has been described above.

This study is indicative of efficacy of Exalief in the treatment of children with partial seizures, however, due to the study design the contribution to the proof of efficacy in the adult epilepsy patients is very limited. Further studies are ongoing and/or planned.

Supportive studies

Long term efficacy trials: out of the 857 subjects who completed part I of studies 301, 302 and 303, 831 (97.0%) entered part II of these studies, an open-label extension trial to evaluate the safety and efficacy of Eslicarbazepine acetate over a 1-year open-label period. Part II of study 301 was completed and studies 302 and 303 were still ongoing at the time of opinion.

In Study 301-II the efficacy parameters remained stable over time, the Exalief dose administered remained stable after the first 4 weeks of treatment.
The discontinuation rate (23.9% of patients) was moderately high, the most common reason was withdrawal of consent (41 patients, corresponding to 13.1%), followed by occurrence of unacceptable AE (10 patients, 3.2%). Exacerbation of seizures occurred in 2 patients (0.6%). However lack of efficacy was not among the pre-defined reasons for withdrawal; it was concluded to be the reason if a patient prematurely discontinued the study due to exacerbation of seizures.

Due to the inevitable selection bias, the missing of a control group and the open-label design, open-label extension studies are naturally of limited value. Therefore, the data concerning health-related questionnaires are not conclusive and inclusion of the respective data into chapter 5.1 of the SPC is misleading.
However, the presented data indicate that the therapeutic effect of eslicarbazepine is maintained over time.

After completion of the open-label extension parts of studies 302 and 303, the applicant should submit the respective efficacy results.

Discussion on clinical efficacy

The three pivotal studies (301, 302 and 303) were essentially similar in design and allowed for an integrated analysis (phase III integrated studies).

With regard to the primary efficacy variable of the three pivotal studies (i.e. the seizure frequency during the maintenance period standardised to 4 weeks) as well as to the responder rate, efficacy of the 800 and 1200 mg daily dose of Exalief could be shown. Results for the 800 mg and 1200 mg dose were statistically significant superior to placebo in the separate analyses of all three single studies as well as in the phase III integrated analysis, except, that in study 303, the responder rate for the 800 mg dose group did not reach statistical significance compared to placebo.

Relative reduction in standardised seizure frequency during the maintenance period was considerably larger for the Exalief treatment groups compared to placebo, the results for the 800 and 1200 mg dose groups being statistically significant.
A dose dependent increase of the therapeutic effect of Exalief was shown with relatively high consistency.
The effect of the 400 mg dose did not reach statistical significance in almost all parameters examined, therefore, 800 mg is applied for as the minimum therapeutic dose.

The analyses of the further secondary efficacy variables showed a level of efficacy of the 800 mg and 1200 mg dose of Exalief which closely matched the results shown in the analysis of the primary endpoint and the responder rate.
However, some inconsistencies of the presented data were seen to be formally assessed and discussed by the applicant.

In the ITT population of the three pivotal studies, there was a higher and dose dependent incidence of early discontinuations due to adverse events during the maintenance period in the Exalief groups (7.1%) compared to the placebo group (1%).
Apparently, in the three single studies as well as in the integrated analysis patients who discontinued treatment prematurely during one of the treatment periods were still categorized as treatment responders for that particular treatment period when their seizure frequency was reduced by 50% or more up to the point of discontinuation.
The requested conservative responder analysis, in which patients who discontinued early are regarded as non-responders, shows a statistically significant higher responder rate for the 800 mg and 1200 mg Exalief groups compared to placebo in the integrated analysis, as well as for study 301 and 302. These results are in line with the original responder analysis in which patients who discontinued treatment prematurely were still categorized as responders when their seizure frequency was reduced by ≥ 50% up to the point of discontinuation. In study 303, the conservative responder analysis revealed a higher percentage of responders in the 800 mg (32.5%) and 1200 mg (35.6%) dose group compared to placebo (23.5%), though the differences were not statistically significant for both dose groups. A further formal assessment of the conservative responder rates in the three pivotal studies did not reveal relevant heterogeneities between the studies. The finding that the difference in percentage of responders of the 800 mg and 1200 mg dose group, respectively compared to the placebo group, was not statistically significant in study 303 is probably based on the lower number of patients in the respective study and does not put in doubt the overall efficacy results of Exalief.

Efficacy analyses concerning simple partial and complex partial seizures demonstrated a relevant effect of the 800 mg and 1200 mg dose on both seizure types. Responder analysis revealed a dose response for both seizure types and analysis of standardised seizure frequency showed a clear dose related effect for complex partial seizures. Efficacy of Exalief in the treatment of secondary generalised seizures was sufficiently justified by the applicant.

The completed open-label extension-study 301-II indicates, that the therapeutic effect of Exalief is maintained over time.

CLINICAL SAFETY

Introduction

The Exalief clinical development program for the indication of Exalief as adjunctive therapy for refractory partial seizures included 22 phase I studies, 2 phase II studies (study 201 performed in adults and study 202 in children and adolescents, respectively), and 3 phase III studies in adults (including a double-blind part I and open-label extension periods).
In addition, 3 phase II studies were performed in adults for the treatment of acute manic episodes and prevention of recurrence of mood episodes in bipolar disorder I.

Information on safety of Exalief in the therapy as adjunctive treatment in adult epilepsy patients is mainly derived from the integrated safety data from part I of the phase III studies 301, 302 and 303 together with the data from study 201 and the completed extension of study 301 part II. All of these studies were performed in the target indication, namely adults with refractory partial seizures.

Furthermore, the clinical pharmacology studies (phase I studies) as well as phase II clinical studies in other than the target indication, i.e. 1 paediatric study (No. 202), 3 studies in patients with bipolar disorder (Nrs. 203, 204 and 205, respectively) and ongoing studies (part II of studies 302 and 303, respectively as well as part III of study 301) provided supportive data to elucidate the safety profile of Exalief.

Patient exposure

At the cut-off date of 30 September 2007 more than 2000 subjects had been exposed to single or repeated doses of Exalief. All Exalief doses were given orally in the clinical studies, either as tablets or as a suspension.

Table 1: Summary of total exposure in ESL clinical program (completed studies)

Development Phase	Subject Population	Number of Studies	Number of Subjects Treated		
			ESL	Placebo	Total
Phase I	Non-epileptic adults	22	558	115	592[a]
Phase II	Adults/Children[b] with refractory partial epilepsy	2	127[b]	47	174
	Adults with bipolar disorder	3	172[c]	51	199[c]
Phase III	Adults with refractory partial epilepsy	3	840	289	1049[d, e]
Total clinical studies		***30***	***1694***	***502***	***2014***

a Due to cross-over designs, numbers treated in Phase I studies are not additive.
b 31 children 2-17 years of age received ESL in Study BIA-2093-202.
c The total column is not cumulative of the ESL and placebo columns due to 24 subjects who received placebo treatment in Studies BIA-2093-203 or -204 and then received ESL in Study BIA-2093-205.
d The total column is not cumulative of the ESL and placebo columns due to 80 subjects who were treated with placebo in Part I of Study BIA-2093-301 and then with ESL in Part II.
e 1 subject in Study BIA-2093-303 was treated with placebo during the 12-week treatment period and then with ESL 400 mg QD for 14 days; this subject is not included in the numbers shown here.

In the open-label extension studies in the target indication (part II of studies 301, 302 and 303) 833 patients received at least one dose of Exalief, 700 patients were exposed to Exalief for ≥ 6 months and 612 patients for ≥ 12 months.

In Phase I studies in healthy subjects Exalief doses up to 3600 mg/day were tested (study No.118), and the identified maximum tolerated dose (MTD) was 2400 mg/day (study No. 113).

In studies in patients with bipolar disorder the maximum daily Exalief dose tested was 2400 mg QD, administered in monotherapy.

Adverse events

TEAEs

Table: Summary of TEAEs - Phase II/III-part I adult epilepsy studies

Type of event	Study 201		Integrated Phase III Studies, Part I				
	Placebo (N=47)	Total ESL (N=96)	Placebo (N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total ESL (N=760)
All TEAEs	21 (44.7)	38 (39.6)	134 (46.4)	119 (60.7)	178 (62.7)	189 (67.5)	486 (63.9)
Possibly related TEAEs	10 (21.3)	23 (24.0)	72 (24.9)	75 (38.3)	134 (47.2)	154 (55.0)	363 (47.8)
SAEs	1 (2.1)	2 (2.1)	4 (1.4)	9 (4.6)	10 (3.5)	9 (3.2)	28 (3.7)
TEAEs leading to discontinuation of study medication	5 (10.6)	9 (9.4)	13 (4.5)	17 (8.7)	33 (11.6)	54 (19.3)	104 (13.7)
Deaths	0	0	1 (0.3)	0	0	0	0

In part I of the phase III studies, the overall incidence of TEAEs increased with increasing doses of Exalief (46.4% placebo, 60.7% 400 mg Exalief, 62.7% 800 mg Exalief and 67.5% 1200 mg Exalief), the dose-dependent increase was also seen for possibly related TEAEs and TEAEs leading to discontinuation of study medication.
The increase in TEAEs was mainly due to a small number of specific events in the Exalief 800 and 1200 mg groups, namely diplopia, nausea, abnormal coordination, dizziness, headache, and somnolence. In addition to vertigo, blurred vision, vomiting, and fatigue, these were the same events that led to an increased incidence of subjects discontinuing in the Exalief groups. TEAEs occurred mainly during the first 6 weeks of treatment.

In general, the profile of at least possibly related TEAEs of the integrated Phase III studies and the (double-blind) study 201 appears similar to that of oxcarbazepine and the apparent frequencies do not raise any serious concern.

In the placebo controlled studies with Exalief in the target indication, some possibly related TEAEs (e.g. headache, diplopia, nausea and vomiting) appear to occur less frequently compared to the known frequencies from oxcarbazepine. However, conclusive results could only be provided from active comparator studies.

Clinically significant hyponatraemia (<125 mmol/L) has occurred uncommonly, however, an evaluation of the frequency of hyponatraemia causing clinical symptoms and the time to onset of hyponatraemia after start of Exalief treatment is missing and should be presented.

The frequency of rash appears to be common, which is in accordance with the incidence of rash known from oxcarbazepine. No definite conclusion concerning the possible risk of serious immune and skin disorders (including Steven-Johnson syndrome) can be drawn and these events will be further followed in the RMP.

Serious adverse events

In part I of the phase III studies there was a somewhat higher (but not dose related) incidence of SAEs in the Exalief groups (3.7%) compared to the placebo group (1.4%).The only SOCs in which more than 2 subjects per Exalief treatment group reported SAEs were nervous system disorders (1, 0.3% placebo; 13, 1.7% Total Exalief) and gastrointestinal disorders (0 placebo; 7, 0.9% Total Exalief).

Table: Serious TEAEs, by decreasing frequency - Phase II/III adult epilepsy studies (safety population)

Preferred term	Number (%) of subjects							
	Study 201		Integrated Phase III Studies, Part I					Study 301 Part II
	Placebo (N=47)	Total ESL (N=96)	Placebo (N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total ESL (N=760)	Total ESL (N=314)
Total subjects with SAEs	**1 (2.1)**	**2 (2.1)**	**4 (1.4)**	**9 (4.6)**	**10 (3.5)**	**9 (3.2)**	**28 (3.7)**	**19 (6.1)**
Coordination abnormal	0	0	0	2 (1.0)	2 (0.7)	1 (0.4)	5 (0.7)	0
Vomiting	0	0	0	1 (0.5)	2 (0.7)	1 (0.4)	4 (0.5)	0
Drug toxicity	0	0	0	1 (0.5)	1 (0.4)	1 (0.4)	3 (0.4)	2 (0.6)
Vertigo	0	0	0	1 (0.5)	1 (0.4)	1 (0.4)	3 (0.4)	1 (0.3)
Diplopia	0	0	0	2 (1.0)	0	0	2 (0.3)	0
Dizziness	0	0	0	1 (0.5)	0	1 (0.4)	2 (0.3)	0
Convulsion	0	0	0	1 (0.5)	1 (0.4)	0	2 (0.3)	1 (0.3)
Cerebellar syndrome	0	0	0	0	0	1 (0.4)	1 (0.1)	0
Constipation	0	0	0	0	0	1 (0.4)	1 (0.1)	0
Gastric disorder	0	0	0	0	0	1 (0.4)	1 (0.1)	0
Hypertensive crisis	0	0	0	0	0	1 (0.4)	1 (0.1)	0
Rash	0	0	0	0	0	1 (0.4)	1 (0.1)	0
Angina pectoris	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Endometriosis	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Follicle centre lymphoma, follicular grade I, II, III	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Gastric ulcer	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Gastroenteritis	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Hyponatraemia	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Renal failure acute	0	0	0	0	1 (0.4)	0	1 (0.1)	0
Complex partial seizures	0	0	0	1 (0.5)	0	0	1 (0.1)	1 (0.3)
Depression	0	0	0	1 (0.5)	0	0	1 (0.1)	0
Grand mal convulsion	0	0	0	1 (0.5)	0	0	1 (0.1)	3 (1.0)
Nervousness	0	0	0	1 (0.5)	0	0	1 (0.1)	0
Psychotic disorder	0	0	0	1 (0.5)	0	0	1 (0.1)	0
Traumatic brain injury	0	0	0	1 (0.5)	0	0	1 (0.1)	1 (0.3)
Vasculitis cerebral	0	0	0	1 (0.5)	0	0	1 (0.1)	0
Death	0	0	1 (0.3)	0	0	0	0	1 (0.3)
Fibroadenoma of breast	0	0	1 (0.3)	0	0	0	0	0
Paraesthesia	0	0	1 (0.3)	0	0	0	0	0
Pneumonia primary atypical	0	0	1 (0.3)	0	0	0	0	0

Preferred term	Number (%) of subjects							
	Study 201		Integrated Phase III Studies, Part I					Study 301 Part II
	Placebo (N=47)	Total ESL (N=96)	Placebo (N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)	Total ESL (N=760)	Total ESL (N=314)
Gastroenteritis viral	1 (2.1)	0	0	0	0	0	0	0
Gastrointestinal infection	0	1 (1.0)	0	0	0	0	0	0
Lymphadenitis	0	0	0	0	0	0	0	1 (0.3)
Otitis media acute	0	0	0	0	0	0	0	1 (0.3)
Head injury	0	0	0	0	0	0	0	1 (0.3)
Thermal burn	0	0	0	0	0	0	0	1 (0.3)
Scull fracture	0	0	0	0	0	0	0	1 (0.3)
Colorectal cancer	0	0	0	0	0	0	0	1 (0.3)
Hemiparesis	0	0	0	0	0	0	0	1 (0.3)
Psychomotor hyperactivity	0	0	0	0	0	0	0	1 (0.3)
Status epilepticus	0	0	0	0	0	0	0	1 (0.3)
Postical state	0	0	0	0	0	0	0	1 (0.3)
Ischaemic stroke	0	1 (1.0)	0	0	0	0	0	0
Delusion	0	0	0	0	0	0	0	1 (0.3)
Delusional disorder, persecutory type	0	0	0	0	0	0	0	1 (0.3)

Events are sorted by decreasing frequency in the Total ESL column of Studies 301, 302, and 303 Part I.

N = total number of subjects; SAE = serious adverse event.

Deaths

In total 10 death cases occurred during the clinical trial programme of Exalief.

During the phase I study BIA-2093-105 a 65 year old patient treated with 600mg Exalief died of cardiovascular failure after occlusion of a coronary artery. A causal relationship with Exalief appears unlikely.

In two of the three phase II studies in adult patients with bipolar disorder two deaths occurred. In study BIA-2093-203, a 42-year-old subject in the placebo group experienced an ischemic stroke. The event was not considered related to study medication. In study BIA-2093-205, a 30-year-old subject committed suicide 5 days after the last 900mg dose of Exalief. The subject had been prematurely discontinued from study due to withdrawal of consent. The investigator considered the event as not related to Exalief treatment.

In part I of the placebo-controlled integrated phase III study BIA-2093-301, a 50-year-old subject in the placebo group died of hypothermia.

During the open label extension periods of the phase III studies six patients died.
In part II of study BIA-2093-301 a 56-year old patient treated with Exalief 800 mg QD, gabapentin 1200 mg/day and valproic acid 1500 mg/day, died of drowning in the bathroom. A causal relationship with Exalief was determined unlikely.

In part II of study BIA-2093-302 one 31-year old subject and one 33-year old subject treated with Exalief 1200mg/day died of drowning. Investigator assessed these two cases as unlikely to be related to Exalief treatment. Another 31-year-old subject treated with Exalief 800 mg QD, levetiracetam 2 g/day and CBZ 400 mg/day, and with several cardiovascular risk factors suffered from a sudden unobserved death and severe coronary atherosclerosis. Investigator assessed this event as a case of sudden unexplained death which was possibly related to Exalief.
In part II of study BIA-2093-303 one 54-year-old subject treated with Exalief 800 mg QD, CBZ 1000 mg/day and LMT 150 mg/day died due to neoplasm recurrence of a previous low grade astrocytoma. The investigator assessed this event as not related to Exalief treatment. Another 33-year-old subject treated with Exalief 800 mg QD, CBZ 800 mg/day and valproic acid 1000 mg/day died of acute respiratory insufficiency and epilepsy grand mal. The investigator assessed this event as possibly related to Exalief.

Whereas it can not completely be ruled out that in two of these patients an increase in seizure frequency caused by Exalief might have contributed to death. However, anticonvulsives are known to increase the seizure frequency in individual patients and Exalief appears not to lead to a relevant increase in seizure frequency.

A 'Risk for suicidality class wording' for anticonvulsants has recently been finalised in the Pharmacovigilance Working Party and the respective information is included in the SPC and PIL.

Toxicological studies in dogs did not reveal a signal with respect to cardiotoxicity. It has been shown that Exalief inhibits voltage-gated sodium channels, however, it is not clarified, whether this inhibition occurs specifically in the central nervous system or not. Inhibition of cardiac sodium channels leads to an increase in QRS-duration, which is associated with sudden death.
In the thorough QT study, the time averaged QRS duration increased of about 0.8 to 1.05 ms (placebo: 0.32 ms) which seems to be not clinically relevant. Furthermore, from the evaluation of the ECG recordings performed during clinical studies with Exalief, no signal towards an increase in QRS interval can be derived.

The thorough QT study did not raise concerns with respect to QT prolongation, and showed a mild and dose dependent increase in the PR interval of about 5-8 ms (placebo: 2 ms) despite of a mild increase in heart rate (neither of which is considered of clinical relevance of its own). Evaluation of ECG recordings performed during clinical trials showed a mean increase in PR interval in Exalief treated patients compared to baseline which was not strictly dose dependent but highest in the 1200 mg dose group with a mean increase in PR interval of 5.5 ±30.6 ms (compared to a slight decrease in the placebo group of -0.8 ± 20.6 ms). The results are in accordance with the finding of the thorough QT study. Thus, administration of Exalief should be absolutely contraindicated in patients with 2nd and 3rd degree atrioventricular block and further evaluation of a population at risk of PR increase under treatment with Exalief should be performed.
However, during the integrated phase III studies and study 201 atrioventricular block (first degree) was registered as TEAE only once after administration of placebo but not after administration of Exalief.

Laboratory findings:
The numbers of clinically significant increases in transaminases which occurred during the integrated phase III studies, part II of study 301, study 201 and phase I studies in Exalief patients compared to placebo patients do not raise serious concerns. However, to include as much data as possible in the evaluation of transaminase increase, all cases which occurred during the other phase II studies (besides study 201) and of part II of studies 302 and 303 should also be listed and evaluated with respect to severity and causal relationship.

Increase in INR should be included in the RMP (increase in aPTT is already included). The potential of Exalief to increase total- and LDL- cholesterol should be closely observed through routine pharmacovigilance.

Safety in special populations
Only very few patients ≥ 65 years have been exposed to Exalief during the phase III studies (9 patients ≥ 65 received Exalief during double blind period of phase III studies). No patient ≥ 65 years received Exalief in the phase II study relevant for the indication (No. 201).
There is a trend towards a higher frequency of all TEAEs and possibly related TEAEs for this age group; however, the number of elderly patients is too small to draw meaningful conclusions. Altogether, Exalief has not been adequately studied in elderly patients and adequate information on the very limited data on Exalief in elderly should be given in the SPC. Moreover, the incidence of epilepsy is the highest in the elderly population and therefore this population will be the most frequently treated population among the target population for therapy with this product. Therefore, the applicant was asked to make a proposal, how the efficacy and safety in the elderly population will be addressed. Next, the applicant is asked to summarize the data, which are expected to be gained post-authorization from the population > 65 years.

Clinical data in patients with mild to moderate hepatic impairment is limited and no pharmacokinetic as well as no clinical data are available in patients with severe hepatic impairment. Therefore, Exalief should only be used with caution in patients mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

Due to the increased extent of exposure to Exalief observed in subjects with renal impairment, dose adjustments are required in these subjects. As only 8 patients in the evaluation of the appropriate cut-off for dose adjustment in renal impaired patients [Memo-Exalief-RenalImpAdjust_05JUN2007] had a Creatinine clearance within the range of 30-60 ml/min reliability of the respective evaluation should be further justified by the applicant. Exalief is not recommended in patients with severe and end-stage renal impairment (Creatinine clearance < 30 ml/min) due to insufficient data.

Safety related to drug-drug interactions and other interactions
Although the incidence of treatment-emergent adverse events (TEAEs) was higher in subjects treated with concomitant CBZ than in subjects not treated with CBZ, this was true for both Exalief and placebo treated subjects. Diplopia was reported more frequently by patients taking Exalief plus CBZ compared to the overall population.

Discontinuation due to adverse events
The percentage of patients discontinuing treatment increases noticeably with increasing dose. Most discontinuations were because of unacceptable AEs which occurred in a treatment- and dose-dependent manner. The increased incidence of subjects discontinuing in the Exalief groups in the integrated Phase III studies was primarily due to events of vertigo, diplopia, blurred vision, nausea, vomiting, fatigue, abnormal coordination, dizziness, headache, and somnolence.

Post marketing experience

There is no post-marketing experience with Exalief.

Overall conclusions on clinical safety

Due to the very close pharmacological relationship of eslicarbazepine acetate with oxcarbazepine (following oral administration of Exalief and oxcarbazepine, respectively, the same active moieties, i.e.S-licarbazepine, R-licarbazepine and oxcarbazepine, are found in plasma, though in somewhat different proportions), it is highly probable, that adverse events, which occur after administration of oxcarbazepine may also occur after administration of Exalief.

In general, the profile of at least possibly related TEAEs which occurred during the integrated Phase III studies and the double-blind phase II study No. 201 appears similar to that of oxcarbazepine and the apparent frequencies do not raise any serious concern.

In the placebo controlled studies with Exalief in the target indication, some possibly related TEAEs (e.g. headache, diplopia, nausea and vomiting) appear to occur less frequently compared to the known frequencies from oxcarbazepine. However, conclusive results could only be provided from active comparator studies.

In part I of the phase III studies, the overall incidence of TEAEs increased with increasing doses of Exalief (46.4% placebo, 60.7% 400 mg Exalief, 62.7% 800 mg Exalief and 67.5% 1200 mg Exalief), the dose-dependent increase was also seen for possibly related TEAEs and TEAEs leading to discontinuation of study medication.
The increase in TEAEs was mainly due to a small number of specific events in the Exalief 800 and 1200 mg groups, namely diplopia, nausea, abnormal coordination, dizziness, headache, and somnolence. In addition to vertigo, blurred vision, vomiting, and fatigue, these were the same events that led to an increased incidence of subjects discontinuing in the Exalief groups.

There was a somewhat higher incidence of SAEs in the Exalief groups (3.7%) compared to the placebo group (1.4%), but the proportion of subjects was similar in each of the Exalief groups. The only SOCs in which more than 2 subjects per group reported SAEs were nervous system disorders (1, 0.3% placebo; 13, 1.7% Total Exalief) and gastrointestinal disorders (0 placebo; 7, 0.9% Total Exalief).

During the clinical development program, 8 death cases occurred in patients treated with Exalief.
From the information provided, a causal relationship with Exalief treatment appears unlikely.
It can not be ruled out that an increase in seizure frequency caused by Exalief in individual patients might have contributed to individual death cases. However, anticonvulsants are known to increase seizure frequency in individual patients and Exalief appears not to lead to a relevant increase in seizure frequency. One Exalief patient died of sudden unobserved death and severe coronary atherosclerosis, in which case a contributory role of Exalief by increase in PR interval at pre-existing atrioventricular block can not be completely ruled out. Evaluation of ECG recordings performed during clinical trials showed a mean increase in PR interval in Exalief treated patients compared to baseline which was not strictly dose dependent but highest in the 1200 mg dose group with a mean increase in PR interval of 5.5 ±30.6 ms (compared to a slight decrease in the placebo group of -0.8 ± 20.6 ms). The results are in accordance with the finding of the thorough QT study. Thus, administration of Exalief is absolutely contraindicated in patients with 2nd and 3rd degree atrioventricular block and caution is advised in patients with medical conditions or co-medication known to be associated with PR prolongation.

However, during the integrated phase III studies and study 201 atrioventricular block (first degree) was registered as TEAE only once after administration of placebo but not after administration of Exalief.

There are no concerns with respect to QT prolongation or QRS-duration.

From the data presented there is no clear sign of a potential of Exalief for cardiovascular or cerebrovascular ischaemic events. However, as patient numbers are too low to draw definite conclusions on these infrequent events, TEAEs with possible cardiovascular or cerebrovascular ischaemic origin have been included in the RMP.

Only very few patients ≥ 65 years have been exposed to Exalief during the phase III studies (9 patients ≥ 65 received Exalief during double blind period of phase III studies). No patient ≥ 65 years received Exalief in the phase II study relevant for the indication (No. 201).
There is a trend towards a higher frequency of all TEAEs and possibly related TEAEs for this age group; however, the number of elderly patients is too small to draw meaningful conclusions. On the other hand, the characteristics of Exalief can be predicted to a large extent based on similarity of Exalief with oxcarbamazepine/carbamazepine. To gain more information, an open-label, 6 month study in approximately 100 patients ≥ 65 years will be performed, respective results will be provided as a follow-up measure.

As clinical data in patients with mild to moderate hepatic impairment is limited and no pharmacokinetic as well as no clinical data are available in patients with severe hepatic impairment, Exalief should be used with caution in patients mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

Due to the increased extent of exposure to Exalief observed in subjects with renal impairment, dose adjustments are required in patients with CL_{CR} 30-60 ml/min and is not recommended in patients with severe and end-stage renal impairment (CL_{CR} <30 ml/min) due to insufficient data.

Hyponatriaemia (<125 mmol/L) occurred uncommonly during the integrated phase III studies.

The frequency of rash appears to be common, which is in accordance with the incidence of rash known from oxcarbazepine. No definite conclusion concerning the risk of serious immune and skin disorders can be drawn and these events will be further followed in the RMP.

Increase in INR and aPTT have been taken into account in the RMP.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

As the applicant had informed the Rapporteurs that a new version of the DDPS was expected end of 2008 (in fulfilment of a commitment made during the validation phase), the Rapporteurs requested the Applicant to include that information on the new version. This new version was submitted by the Applicant in December 2008 and is assessed as follows:

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 3.0 dated 12 December 2008). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan:

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hyponatraemia	Routine pharmacovigilance activities. Systematically collected and analysed in ongoing clinical studies. Information will be reported and evaluated in PSURs	Listed in the SPC (section 4.8) Warning in Section 4.4 of the SPC "Hyponatraemia has been reported as an adverse reaction in less than 1% of patients treated with Exalief. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate dose. In patients

		with pre-existing renal disease leading to hyponatraemia, or in patients concomitantly treated with medicinal products which may themselves lead to hyponatraemia (e.g. diuretics, desmopressin), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically relevant hyponatraemia develops, Exalief should be discontinued"
Cutaneous adverse reactions Stevens Johnson	Routine pharmacovigilance activities. Systematically collected and analysed in ongoing as well as future clinical studies. Systematic collection of detailed information regarding cutaneous adverse reactions through a specific questionnaire (Annex 7) Systematic check of return of the questionnaire Information will be reported and evaluated in PSURs The relevance of HLA data to the prevention of the Stevens Johnson syndrome will be discussed in PSURS for each Stevens Johnson/TEN case	Listed in the SPC (section 4.3 and 4.8) It includes information to stop therapy in case of signs or symptoms of hypersensitivity (section 4.4). Warning in Section 4.4 of the SPC "Rash developed as an adverse reaction in 1.1% of total population treated with Exalief in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, Exalief must be discontinued." Warning in Section 4.4 of the SPC "No cases of serious cutaneous reactions have been reported with eslicarbazepine acetate. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Therefore, whenever possible, subjects of Han Chinese and Thai origin should be screened for this allele before starting treatment with carbamazepine or chemically-related compounds. The presence of HLA-B*1502 allele in other ethnicities is negligible. The allele HLA-B*1502 is not associated to SJS in the Caucasian population."
Thyroid function changes	Routine pharmacovigilance activities. Systematically collected and analysed in ongoing clinical studies. Information will be reported and evaluated in PSURs	No particular risk minimization activity is considered necessary. Hypothyroidism reported as an ADR was uncommon (frequency ≥1/1000 to <1/100).

INR and aPTT increase	Systematically collected and analysed in ongoing clinical studies. Regular reporting in PSURs.	No particular risk minimization activity is considered necessary No detailed action plan for specific safety concerns is deemed necessary.
Cardiovascular/cerebrovascular ischaemia	Routine pharmacovigilance activities. Systematically collected and analysed in ongoing as well as future clinical studies. Systematic collection of data of cardiovascular/cerebrovascular serious adverse reactions through a specific questionnaire (annexed in the RMP). Systematic check of return of the questionnaire Information will be reported and evaluated in PSURs.	No particular risk minimization activity is considered necessary
Potential for suicidality as anti-epileptic drug	Routine pharmacovigilance activities. Systematically collected and analysed in ongoing clinical studies in adults (Phase III studies) through MADRS Information will be reported and evaluated in PSURs	Warning in Section 4.4 of the SPC «Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic active substances in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Exalief. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.»
Exposure during pregnancy	Systematic collect registry of pregnancy reports in routine pharmacovigilance. Establish a Pregnancy Registry in order to identify and characterise safety concerns. A protocol of the registry will be submitted by July 2009	Specific information is included in section 4.6 of the SPC that caution should be exercised when prescribing Exalief to pregnant or lactating women. <u>Risk related to epilepsy and antiepileptic medicinal products in general</u> It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3 % in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neutral tube defects. Multiple antiepileptic medicinal product

		therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both, mother and child. Risk related to Exalief There are no data from the use of Exalief in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). If women receiving Exalief become pregnant or plan to become pregnant, the use of Exalief should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening. Monitoring and prevention Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid. In the newborn child Bleeding disorders in the newborn caused by antiepileptic medicinal products have been reported. As a precaution, vitamin K1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn. Women of childbearing potential/contraception Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and

		safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped. It is unknown whether eslicarbazepine acetate is excreted in human breast milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with Exalief.
Paediatric population	Routine pharmacovigilance activities. A double blind, placebo controlled phase III study (Study code BIA-2093-305) in approximately 250 children aged from 2 to 16 years with refractory partial epilepsy to evaluate efficacy and safety of Exalief in this population is ongoing. A phase II study (Study code BIA-2093-208) to evaluate the effects of Exalief on cognition in comparison with placebo as adjunctive therapy in approximately 90 children aged 6 to 16 years old with refractory partial-onset seizures is being implemented.	A warning is included in section 4.2 of the SPC that Exalief is not recommended for use in children until further data become available. "Paediatric population Exalief is not recommended for use in children below 18 years due to a lack of data on safety and efficacy."
Elderly population	Routine pharmacovigilance activities. An open-label study (Study Code BIA-2093-401) evaluating Exalief as add-on therapy in approximately 100 subjects ≥65 years is planned to be implemented in 2009. The basic study design will consist of an 8-week baseline period followed by a 6-month treatment period in which Exalief will be titrated in the dose range of 400-1200 mg according to clinical response. To be admitted in the study subjects should have at least 2 seizures per month despite treatment with 1 or 2 AEDs given in therapeutic doses.	A warning is included in section 4.2 of the SPC that Exalief should be used with caution in elderly subjects. Elderly (over 65 years of age) Caution should be exercised in the treatment of elderly patients as there is limited safety information on the use of Exalief in these patients.
Missing information Interactions inducing properties of Exalief	Routine pharmacovigilance activities. The following clinical trials are planned for 2009: **BIA-2093-129:** Pharmacokinetic interaction study between Exalief	Specific information is included in section 4.5 of the SPC "Exalief is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl

on: - CYP 3A4 - Carbamazepine	and carbamazepine in healthy subjects **BIA-2093-124**: Effect of repeated administration of Exalief on the pharmacokinetics of simvastatin in healthy subjects	transferases. Therefore, *in vivo* eslicarbazepine may have an inducing effect on the metabolism of medicinal products which are mainly eliminated by metabolism through CYP3A4 or conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Exalief or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. This time delay must be taken into account when Exalief is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Exalief. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of Exalief with medicinal products that are mainly metabolised by CYP2C19.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 the clinic.

Non-clinical pharmacology and toxicology

Information on the non-clinical pharmacology, pharmacokinetics and toxicology has been presented in a satisfactory manner. No unexpected or unduly worrying findings have been evidenced. The Applicant has committed to perform post-approval studies to complete the environmental risk assessment, including a water sediment study.

Efficacy

In three pivotal efficacy studies with parallel group design, Exalief in doses of 400 mg/day, 800 mg/day or 1200 mg/day was added to 1 to 3 concomitant antiepileptic drugs.

With regard to the primary efficacy variable of the three pivotal studies (i.e. the seizure frequency during the maintenance period standardised to 4 weeks) as well as to the 50% responder rate (the relative change in standardised seizure frequency ≥50% in comparison to baseline period.), efficacy of the 800 and 1200 mg daily dose of Exalief could be shown. The respective results for the standardised seizure frequency for the 800 mg and 1200 mg dose were statistically significant superior to placebo in the separate analyses of all three single studies as well as in the phase III integrated analysis.

Standardised seizure frequency - Phase III integrated studies in the ITT population:

	Baseline Period			Maintenance Period		
Treatment	**N**	**Mean±SD**	**Median**	**N**	**Mean±SD**	**Median**
Placebo	286	12.9±16.82	7.0	279	**11.7±17.85**	6.4
Exalief 400 mg	195	13.0±15.08	8.0	192	**10.6±13.11**	5.9
Exalief 800 mg	282	13.4±15.31	7.7	262	**9.8±14.79**	5.0
Exalief 1200 mg	272	13.3±15.26	8.0	253	**9.0±13.10**	4.6

Responder analysis - Phase III integrated studies in the ITT population:

	N	Number (%)	Odds ratio		Relative Risk	
Treatment		**of responders**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Placebo	279	60 (21.5)	-	-	-	-
Exalief 400 mg	192	44 (22.9)	**1.25**	**(0.77, 2.04)**	**1.19**	**(0.81, 1.76)**
Exalief 800 mg	262	95 (36.3)	**2.08**	**(1.42, 3.04)**	**1.69**	**(1.28, 2.22)**
Exalief 1200 mg	253	110 (43.5)	**2.81**	**(1.92, 4.10)**	**2.02**	**(1.55, 2.63)**

The effect of the 400 mg dose did not reach statistical significance in almost all parameters examined; therefore, 800 mg is applied for as the minimum therapeutic dose. A dose dependent increase of the therapeutic effect of Exalief was shown with relatively high consistency.

Efficacy analyses concerning simple partial and complex partial seizures demonstrated a relevant effect of the 800 mg and 1200 mg dose on both seizure types and efficacy of Exalief on secondary generalized seizures was sufficiently justified by the applicant.

Taken the results of the 3 open-label extension-studies altogether, it appears the therapeutic effect of Exalief is maintained over time.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Due to the very close pharmacological relationship of eslicarbazepine acetate with oxcarbazepine (following oral administration of Exalief and oxcarbazepine, respectively, the same active moieties, i.e. eslicarbazepine, R-licarbazepine and oxcarbazepine, are found in plasma, though in somewhat different proportions), it is highly probable, that adverse events, which occur after administration of oxcarbazepine may also occur after administration of Exalief.

In general, the profile of at least possibly related TEAEs which occurred during the integrated Phase III studies and the double-blind phase II study No. 201 appears similar to that of oxcarbazepine and the apparent frequencies do not raise any serious concern.
In the placebo controlled studies with Exalief in the target indication, some possibly related TEAEs (e.g. headache, diplopia, nausea and vomiting) appear to occur less frequently compared to the known frequencies from oxcarbazepine. However, conclusive results could only be confirmed from active comparator studies.

Evaluation of ECG recordings performed during clinical trials showed a mean increase in PR interval in Exalief treated patients compared to baseline which was not strictly dose dependent but highest in the 1200 mg dose group with a mean increase in PR interval of 5.5 ±30.6 ms (compared to a slight decrease in the placebo group of -0.8 ± 20.6 ms). The results are in accordance with the finding of the

thorough QT study. Thus, administration of Exalief is absolutely contraindicated in patients with 2nd and 3rd degree atrioventricular block and caution is advised in patients with medical conditions or co-medication known to be associated with PR prolongation.
There are no concerns with respect to QT prolongation or QRS-duration.

Only very few patients ≥ 65 years have been exposed to Exalief during the phase III studies. To gain more information, an open-label, 6 months study in approximately 100 patients ≥ 65 years will be performed, respective results will be provided as a follow-up measure.

As clinical data in patients with mild to moderate hepatic impairment is limited and no pharmacokinetic as well as no clinical data are available in patients with severe hepatic impairment, Exalief should be used with caution in patients mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

Dose adjustments are required in patients with CL_{CR} 30-60 ml/min and is not recommended in patients with severe and end-stage renal impairment (CL_{CR} <30 ml/min) due to insufficient data.

Hyponatriaemia (<125 mmol/L) occurred uncommonly during the integrated phase III studies.

The frequency of rash appears to be common, which is in accordance with the incidence of rash known from oxcarbazepine. No definite conclusion concerning the possible occurrence of serious immune and skin disorders (including Steven-Johnson syndrome) can be drawn and these events will be further followed in the RMP.

Increase in INR and aPTT have been included in the RMP.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant has submitted results from user testing of the package leaflet, which was performed in English. During the testing requested information to all questions was located by at least 80 % of participants; all questions were correctly answered by 100 % of participants, who were able to locate the requested information. Overall, the user test is found acceptable. The results demonstrated a sufficient percentage of identification and comprehension of product related information. Therefore, the package leaflet was considered to be in line with the current readability requirements.

Risk-benefit assessment

With regard to the primary efficacy variable of the three pivotal studies (i.e. seizure frequency during the maintenance period standardised to 4 weeks) and the 50% responder rate, efficacy of the 800 mg and 1200 mg dose of Exalief could be demonstrated.

The benefits with Exalief are the fact that, added to concomitant antiepileptic drugs it decreases the standardised frequency of seizures per month (median) from 7.7 to 5.0 on Exalief 800 mg and from 8.0 to 4.6 on Exalief 1200mg, versus a decrease from 7.0 to 6.4 seizures observed in the placebo group.

The percentage of responders (patients with a relative change in standardised seizure frequency ≥50% in comparison to baseline period) is also improved by Exalief: 36.3% on Exalief 800mg and 43.5% on Exalief 1200mg, versus only 21.5% observed in the placebo group.

A dose dependent increase of the therapeutic effect of Exalief was shown with relatively high consistency.

In general, the profile of at least possibly related TEAEs which occurred during the integrated Phase III studies and the double-blind phase II study No. 201 appears similar to that of oxcarbazepine. TEAEs (especially possibly related TEAEs and TEAEs leading to withdrawal) increased with increasing doses of Exalief.
800 mg of Exalief which is regarded the primary target dose, therefore offers the best benefit to risk ratio of the doses tested. Dependent from effectiveness and tolerability the dose may further be increased to 1200 mg.

The benefit/risk balance of Exalief (eslicarbazepine acetate) as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation, is considered to be positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Exalief in the adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation was favourable and therefore recommended the granting of the marketing authorisation.