CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022416Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW-ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 22416	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 11, 2013		
Division:	Division of Neurology Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Sunovion Pharmaceuticals Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	To be determined	**Date Assigned:**	February 11, 2013
Generic Name:	Eslicarbazepine Acetate Tablets	**Date of Review:**	October 17, 2013
Indication:	Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older	**Type of Submission:** 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Immediate release tablet/ 200 mg/tablet, 400 mg/tablet, 600 mg/tablet, and 800 mg/tablet		
Route of Administration	Oral		

SUMMARY

Background: The proposed drug product is an immediate release tablet containing eslicarbazepine acetate as the active ingredient, indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older. This 505(b)(1) New Drug Application was originally submitted on 3/30/2009 for the 400 mg/tablet, 600 mg/tablet, and 800 mg/tablets strengths, and received a complete response letter on 4/30/2010, due to clinical concerns.

Submission: On 9/4/2012, the Applicant resubmitted the NDA and included an additional 200 mg/tablet strength. The first resubmission was considered an incomplete response as stated in a letter from the FDA dated 11/2/12. Therefore, the Applicant submitted a second resubmission to the NDA on 2/11/13.

Review: ONDQA-Biopharmaceutics reviewed the resubmission dated 2/11/13, and a Biopharmaceutics review authored by Dr. Elsbeth Chikhale was placed in DARRTS on 8/27/13. The review dated 8/27/13 concluded that

"The dissolution profile comparison data do not support the approval of the biowaiver request for the 200 mg tablet and therefore the Biowaiver request is not granted. From the Biopharmaceutics perspective the proposed 200 mg strength tablet is not acceptable".

Reference ID: 3391875

For additional information on the Biopharmaceutics evaluation of the dissolution method, dissolution acceptance criterion, (b) (4) for the 400 mg, 600 mg, or 800 mg strengths, please refer to the Original Biopharmaceutics review.

This current document is an **Addendum** to the original Biopharmaceutics review in DARRTS. This review addendum is mainly focused on the evaluation and acceptability of:

1. **The biowaiver request for the lower 200 mg strength, the bridging of the formulations and manufacturing sites**
2. **The dissolution acceptance criterion for the 200 mg tablet strength**
3. **The dissolution data supporting the 200 mg tablet splitting**

1. Biowaiver Request

The recommendation denying the biowaiver for the 200 mg tablet was conveyed to the Applicant on 9/5/13 via Email. The Applicant responded to this Email by providing BA/BE information from previously conducted studies and dissolution profile comparison data for the 200 mg clinical and commercial products. After evaluating this information, additional tablet (b) (4) data were requested on 9/26/13. Upon review of the additional tablet (b) (4) dissolution, and in vivo BA/BE data supporting an indirect bridge of the formulations, ONDQA-Biopharmaceutics decided that the overall in vitro and in vivo information was adequate to support the approval of the Biowaiver request for the 200 mg tablets. During a telephone conference on 9/27/13, the Applicant was informed of the approval of the biowaiver request for the 200 mg.

2. Dissolution Acceptance Criterion

Since the dissolution rate of the 200 mg is (b) (4) the other strengths, in the 9/27/13 teleconference the Applicant was requested to submit their proposal for a revised dissolution acceptance criterion for the 200 mg strength tablets along with supportive dissolution data. On 10/11/13, an agreement between FDA and the Applicant was reached on a dissolution acceptance criterion of Q = (b) (4) at 15 minutes for the 200 mg strength.

RECOMMENDATION:

- The overall in vitro (b) (4) and in vivo BA/BE information supporting the Biowaiver request for the 200 mg strength tablet is acceptable and the Biowaiver is granted.
- The following dissolution method and acceptance criterion are acceptable for the 200 mg tablets.

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Eslicarbazepine acetate	IR Tablet	USP 2 (Paddle)	100	1000 mL pH 4.5 acetate buffer at 37°C	Q = (b) (4) at 15 minutes

- The provided data support the splitting of the 200 mg tablets.

Reference ID: 3391875

From the Biopharmaceutics perspective, NDA 22416 for Eslicarbazepine Acetate Tablets containing 200, 400 mg, 600 mg, or 800 mg eslicarbazepine acetate per tablet is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: RLostritto

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

BIOWAIVER REQUEST/BRIDGING OF DIFFERENT FORMULATIONS:

Background: [redacted] (b) (4) The pivotal phase 3 FC, FN and FK formulations were linked to the to-be-marketed, commercial FP formulation by comparative bioavailability studies. In addition to the formulation changes, a drug product manufacturing site change occurred during the drug product development. All drug product batches for formulations FC, FN, FK, and FO were manufactured in BIAL. For the final to-be-marketed commercial FP formulation, there are drug product batches of each strength that were manufactured in [redacted] (b) (4) as well as in BIAL. Clinical trials, including BA studies, for the 400, 600 and 800 mg tablets used drug product batches from both manufacturing sides.

However, clinical trials for the 200 mg tablets only used drug product batches manufactured in BIAL. There are no BA data available for to-be-marketed FP formulation of the 200 mg tablets manufactured by [redacted] (b) (4) Therefore, the Applicant submitted a formal request for a Biowaiver for the eslicarbazepine acetate 200 mg tablets in an amendment dated 6/28/13.

For previous details, see Original ONDQA-Biopharmaceutics review dated 8/27/13.

Assessment of Biowaiver Request: The provided comparative dissolution data showed failed similarity f2 values between the 200 mg drug product batch with formulation FP, manufactured at [redacted] (b) (4) (CGGM) vs. the 400 mg, 600 mg, and 800 mg tablet batches with formulation FP that were used in clinical studies (batches PD269M-001, PD270M-001, PD271-001, and TXB). Therefore, the Biowaiver for the 200 mg tablets was not supported by the provided dissolution data and the biowaiver for this strength was not granted. On 9/5/13, the Applicant was informed via Email that the biowaiver for the 200 mg tablet was not granted. The following recommendation was sent.

> *Upon review of the provided information supporting your biowaiver request, we have determined that this information does not support the approval of your request for a waiver of the requirement to conduct an in vivo BA/BE study for the 200 mg strength of your proposed drug product and therefore the biowaiver is NOT granted. You need to submit data from a BA/BE study to support the approval of the 200 mg tablet.*

On 9/12/13 the Applicant responded via Email to the above biowaiver recommendation. In their response, they refer to the indirect bridge between the 200 mg drug product batch with formulation FP, manufactured at [redacted] (b) (4) and the 800 mg tablet batches with formulation FP and FC that were used in clinical study. The Applicant has also submitted comparative dissolution profiles showing similarity (f2>50) between 200 mg FO (manufactured in BIAL) and 200 mg FP (manufacturing site was not specified) and they stated that the 200 mg FO (4x) was shown to be bioequivalent to the 800 mg FC (study BIA-2093-109), which in turn is bioequivalent to 800 mg FP (study BIA-2093-122).

To clearly understand the indirect bridge between the Commercial FP (200 mg) - Clinical FO (200 mg) – Clinical FC (800 mg) – Commercial FP (800 mg), a schematic representation of this bridging among the formulations is depicted below:

The most likely cause for the difference in the dissolution profiles between the 200 mg and the 400, 600, and 800 mg strengths causing the failed f2 dissolution comparisons, is (b) (4)

In order to show that the bioequivalence between these batches was demonstrated despite the difference in tablet (b) (4) the Applicant was asked to provide additional information on the (b) (4) of the tablets used in these bioequivalence studies. On 9/26/13, the following IR was sent to the Applicant via Email.

Provide the tablet (b) (4) of the tablets used in the following BA/BE studies:

- *The 800 mg FC tablets and 800 mg FP tablets used in BIA-2093-117 and BIA-2093-122 study*
- *The 800 mg FC tablets and the 200 mg FO tablets used in the BIA-2093-109 study*

The Applicant provided the requested information on 9/27/13:

	Formulation	**800 FP**	**800 FC**		**200 FO**
	Batch number	**PD271M-001**	**060179-L**	**040013-L**	**040012-L**
Specification	(b) (4)				

[aa] Minimum and maximum in-process results. Certificate of Analysis states result is (b) (4)

These data show that the 200 mg FO tablets (b) (4) were bioequivalent to 800 mg FC tablets (b) (4) It should be noted that the 200 mg FP tablets have a (b) (4) which is similar to the 200 mg FO tablets (b) (4) Taking into consideration all available information indicating that although the differences in tablet (b) (4) have an effect on the dissolution rate, these differences do not affect the in vivo performance of the products as demonstrated by the results of the bioequivalence studies, the biowaiver request for the 200 mg tablets is adequate.

On 9/27/13, a teleconference was held with the Applicant to discuss the approval of the 200 mg tablets. During this teleconference the Biowaiver request for the 200 mg tablets was granted based on the following reasons:

1. *The results from the in vivo Bioavailability (BA)/Bioequivalence (BE) studies demonstrating bioequivalence between the following clinical and commercial products.*
   - *BIA-2093-122 (evaluated FC 800 mg vs. FP 800 mg), and*
   - *BIA-2093-109 (evaluated FC 800 mg vs. FO 200 mg)*

2. *Although the in vitro dissolution profile comparison data in different pH media did not support the approval of the Biowaiver request for the 200 mg tablet, the overall in vivo*

data from the above BA/BE studies demonstrate that the products are bioequivalent and therefore the differences in formulation between the FC 800 mg vs. FP 800 mg and differences in dissolution and tablet (b) (4) *between the FC 800 mg vs. FO 200 mg strengths do not extrapolate to the in vivo bioavailability (Cmax and AUC) of the product.*

Overall Assessment: SATISFACTORY

DISSOLUTION ACCEPTANCE CRITERION:

Since the dissolution rate of the 200 mg is (b) (4) the other strengths, during the 9/27/13 teleconference the Applicant was requested to submit a proposal for a revised dissolution acceptance criterion for the 200 mg strength tablets along with supportive dissolution data. On 10/11/13, an agreement between FDA and the Applicant was reached on a dissolution acceptance criterion of Q = (b) (4) at 15 minutes for the 200 mg strength.

Assessment: SATISFACTORY

TABLET SPLITTING:

See Original ONDQA-Biopharmaceutics dated 8/27/13.

Even though there is no proposed dose of 100 mg, from clinical perspective a score on the 200 mg tablet, giving the ability to split a 200 mg tablet in half, is useful for administering a 500 mg or 700 mg dose. The provided data indicate that the proposed 200 mg tablet can be split.

Assessment: SATISFACTORY

RECOMMENDATION:

For the Biopharmaceutics evaluation of the 400 mg, 600 mg, or 800 mg Eslicarbazepine Acetate Tablets, refer to the Original ONDQA-Biopharmaceutics review dated 8/27/13.

The overall conclusions below are for the 200 mg tablet.

- The following dissolution method and acceptance criterion are acceptable for the 200 mg, tablets:

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Eslicarbazepine acetate	IR Tablet	USP 2 (Paddle)	100	1000 mL pH 4.5 acetate buffer at 37°C	(b) (4) (Q) after 15 minutes

- Biowaiver/Bridging of the strengths, manufacturing sites, formulations:
  The Biowaiver request for the 200 mg strength tablet is acceptable and the Biowaiver is granted.

- Tablet splitting of the 200 mg tablets:
  The provided data support the splitting of the 200 mg tablets.

From the Biopharmaceutics perspective, NDA 22416 for Eslicarbazepine Acetate Tablets is recommended for **APPROVAL**.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELSBETH G CHIKHALE
10/17/2013

ANGELICA DORANTES
10/17/2013

Clinical Pharmacology Review

NDA#	22416
Date of Original submission:	March 29, 2009
Date of Resubmission:	Aug 31, 2012; Feb 8, 2013
Brand Name:	Aptiom
Generic Name:	Eslicabazepine Acetate
Strength and Formulation:	200, 400, 600, and 800 mg tablets
Sponsor:	Sunovion
Indication:	Adjunctive therapy in the treatment of partial-onset seizures in adults
Submission Type:	Response to CR, Standard.
CP Reviewer Team:	Bei Yu, Ph.D., Angela Men, M.D., Ph.D., Hongshan Li, Ph.D., Atul Bhattaram, Ph.D.

TABLE OF CONTENTS

Reference ID: 3374277

1. EXECUTIVE SUMMARY

Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel and t-type calcium channel blocker with anticonvulsant activity. It was designed to constitute a third-generation, single-enantiomer member of the long established family of first-line dibenz[b,f]azepine antiepileptic drugs (AEDs) represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). It's a prodrug of eslicarbazepine, which is the drug entity responsible for the pharmacological effect.

The sponsor submitted the original NDA in March 2009 for the indication of "adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy". The agency issued the Complete Response Letter on April 30, 2010 due to profound and extensive deficiencies in the conduct and documentation of the study, as well in the presentation of the data in the application. OCP also provided specific comments in the letter, "You should consider developing a lower strength (200 mg) of Stedesa to allow everyday dosing during the titration phase in patients with severe renal impairment. Lower strengths are also appropriate for use in the elderly population."

From a clinical pharmacology perspective, the original NDA was acceptable based on the review conducted by OCP reviewers Drs. Veneeta Tandon, Kofi Kumi, and Joo-Yeon Lee. For the detailed information, please refer to their OCP review in DARRTS.

In the current resubmission, the sponsor provided information based on in vitro dissolution profile studies to support a new 200 mg strength tablet. The sponsor also submitted additional nine clinical pharmacology studies. A new Phase III study (2093-304 Part 1) conducted jointly by Sunovion and BIAL – Portela (Bial) to evaluate the safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures when given once daily at doses of 800 mg and 1200 mg.

1.1 RECOMMENDATION

The NDA resubmission is acceptable from a Clinical Pharmacology perspective and the OCP recommends approval for NDA 22416 pending satisfactory agreement with the sponsor on the label.

1.2 PHASE IV COMMITMENT/REQUIREMNT

None.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY

This section only focuses on the current resubmission based on the new additional studies. For the other detailed clinical pharmacology information, please refer to Dr. Tandon's review in DARRTS (Ref: OCP NDA Review, NDA 22-416, Dr. Veneeta Tandon, 2010).

Exposure-response for efficacy and safety:
ESL 800 - 1200 mg QD is efficacious as an adjunctive therapy in the treatment of partial-onset seizures in adult patients. AEs are dose-dependent.

BE/BA:

Reference ID: 3374277

The PK of 800 mg tablet of ESL is comparable between the intact tablet and the crushed tablet. ESL can be taken as crushed tablets.

200 mg dose strength:
ONDQA does not recommend approval of 200 mg dose strength due to the inadequate dissolution data.

Drug-drug interactions:
Carbamazepine (CBZ): AUC and Cmax of eslicarbazepine decreased by 32% and 22% following the concomitant administration with CBZ at 400 mg BID compared to the administration of ESL alone, respectively. Concomitant oral once-daily administration of ESL 800 mg with CBZ did not affect the carbamazepine and carbamazepine-epoxide kinetic profile. A higher dose of ESL may be necessary when CBZ is concomitantly administered with ESL based on patients' tolerability and need for additional seizure control. However, a greater risk of AEs should be cautious during the concomitant use.

Statins: ESL (800 mg QD) decreased systemic exposures (Cmax and AUC) of simvastatin (80 mg single dose) by 61% and 49%, respectively, and its active metabolite (simvastatin β-hydroxyacid) by 41% and 53%, respectively; ESL (1200 mg QD) decreased systemic exposure (Cmax and AUC) of rosuvastatin (40 mg single dose) by 36% and 39%, respectively. Dose adjustment of simvastatin or rosuvastatin might be needed, if a clinically significant change in lipid is noted.

Contraceptive (Microginon®, ethinyloestradiol and levonorgestrel): 800mg and 1200mg ESL QD decreased levonorgestrel AUC by 11% and 37%; and decreased ethinyloestradiol AUC 25% and 42%, respectively. Additional or alternative non-hormonal birth control should be used.

Drug Distribution in CSF:
Less fluctuation of eslicarbazepine (BIA 2-194) concentration from peak to trough in CSF than in plasma was observed in both ESL (41% v.s., 113%) and OXC (14% v.s., 39%) treatment groups.

PK in pediatrics:
Similarly to what occurs in adult subjects, ESL was rapidly metabolized to BIA 2-194 (S-licarbazepine), the major metabolite. Plasma levels of the parent drug usually remained below the limit of quantification, and BIA 2-195 (R-licarbazepine) and Oxcarbazepine were minor metabolites. Eslicarbazepine (BIA 2-194) showed dose-proportional pharmacokinetics in epileptic children of different age groups treated with ESL concomitantly with anti-epileptic drugs.

Signatures
Bei Yu (CP primary reviewer)
Angela Men (CP TL)
Division of Clinical Pharmacology 1
Hongshan Li (PM reviewer)
Atul Bhattaram (PM TL)

Reference ID: 3374277

2 QUESTION BASED REVIEW (QBR)

This section only focuses on the current resubmission including the new additional studies' results. For the other detailed clinical pharmacology information, please refer to Dr. Tandon's review in DARRTS (Ref: OCP NDA Review, NDA 22-416, Dr. Veneeta Tandon, 2010).

2.1 Specific Questions

2.1.1 Can ESL be taken as crushed tablets?

Yes. Study SEP093-155 compared PK profiles of ESL, eslicarbazepine and (R) - licarbazepine between an intact tablet and a crushed tablet at 800 mg dose strength of ESL. 90% CI of the AUC and Cmax fell into 80-125% for eslicarbazepine when administered an intact table or crushed tablet of 800 mg. The mean values of eslicarbazepine t1/2 were similar between crushed and intact tablets (10.20 vs. 10.31 hours). The study showed that the PK of 800 mg tablet of ESL is BE between the intact tablet and the crushed tablet. ESL can be taken as crushed tablets.

2.1.2 Are there any DDI between ESL and carbamazepine? If yes, is there a need for dosage adjustment?

Yes. The sponsor conducted a dedicated DDI study (BIA-2093-129) between ESL at 800 mg QD and carbamazepine (CBZ) at 400 mg BID. The study showed that AUC and Cmax of eslicarbazepine decreased by 32% and 22% following the concomitant administration with CBZ at 400 mg BID compared to the administration of ESL alone, respectively. Concomitant oral once-daily administration of ESL 800 mg with CBZ did not affect the carbamazepine and carbamazepine-epoxide kinetic profile. The similar result was also shown in the primary submission which was evaluated using a PPK approach.

Thus, from PK perspective, a higher dose of ESL may be necessary. However, TEAEs in the nervous system disorders tended to be more frequent when ESL was coadministered with CBZ than when CBZ was administered alone in the study. Additionally, based on other clinical studies, patients' AEs were more common among patients taking concomitant carbamazepine than other concomitant AEDs. Therefore, the increase of AEs following concomitant CBZ is more likely due to a PD interaction but not a PK interaction between ESL and CBZ.

Therefore, a higher dose of ESL may be necessary when CBZ is concomitantly administered with ESL. However, a greater risk of AEs should be cautious during the concomitant use.

2.1.3 Are there any effects of ESL on the PK of statins? If yes, is there a need for dosage adjustment?

Yes. The sponsor evaluated the effect of ESL on the PK of simvastatin (Study BIA-1093-124) and rosuvastatin (Study BIA-2093-150) in the resubmission. The studies showed that ESL (800 mg QD) decreased systemic exposures (Cmax and AUC) of simvastatin (80 mg single dose) by 61% and 49%, respectively, and its active metabolite (simvastatin β-hydroxyacid) by 41% and 53%, respectively; ESL (1200 mg QD) decreased systemic exposure (Cmax and AUC) of rosuvastatin (40 mg single dose) by 36% and 39%, respectively.

Dose adjustment of simvastatin or rosuvastatin might be needed, if a clinically significant change in lipid is noted.

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2.1.4 Are there any effects of ESL on the PK of oral contraceptive (Microginon®, ethinyloestradiol and levonorgestrel)? If yes, is there a need for dosage adjustment?

Yes. The sponsor conducted a DDI study (Study BIA-2093-128) to evaluate the effect of ESL at 800 mg QD on the PK of a combined oral contraceptive (Microginon ®, 30 µg ethinyloestradiol and 150 µg levonorgestrel). The study showed that ESL of 800 mg QD decreased values of AUC of levonorgestrel and ethinyloestradiol by 11% and 25%, respectively. Another DDI study between ESL of 1200 mg QD and single dose of Microginon ® in the primary submission also showed that ESL decreased values of AUC of levonorgestrel and ethinyloestradiol by 37% and 42%, respectively.

Thus, additional or alternative non-hormonal birth control should be used.

2.1.5 Should (b) (4) information be included in the ESL label?

(b) (4)

Therefore, the language (b) (4) should not be included under Section 12.3 in the proposed label.

2.1.6 What is the dose adjustment for moderate and severe renal impairment?

The systemic exposure (AUC) to eslicarbazepine was increased by 62%, 116% and 154% in the mild, moderate, and severe renal impairment groups, respectively, in comparison to that of the healthy subjects. 200mg strength development was recommended in the original review cycle for moderate and severe renal impaired patients. In this submission, although the sponsor developed 200 mg dose strength, due to the inadequate dissolution data, 200 mg dose strength will not be approved. (b) (4) (Ref: OCP NDA Review, NDA 22-416, Dr. Veneeta Tandon, 2010).

2.1.7 What is the PK behavior of eslicarbazepine in pediatric patients?

A multiple-dose PK study in 30 pediatric patients at three different age groups (2-6 yrs, 7-11 yrs, and 12-17 yrs) was conducted. The study was constituted by a 4-week baseline phase, followed by 3 consecutive 4-week treatment periods with eslicarbazepine acetate in which patients received eslicarbazepine acetate once-daily at following dosage regiments: 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). As it has seen in adults, ESL was rapidly metabolized to BIA 2-194 (S-licarbazepine), the major

metabolite; and R-licarbazepine and oxcarbaxepine were minor metabolites in pediatric patients. Dose-proportionality of eslicarbazepine was observed in all age groups.

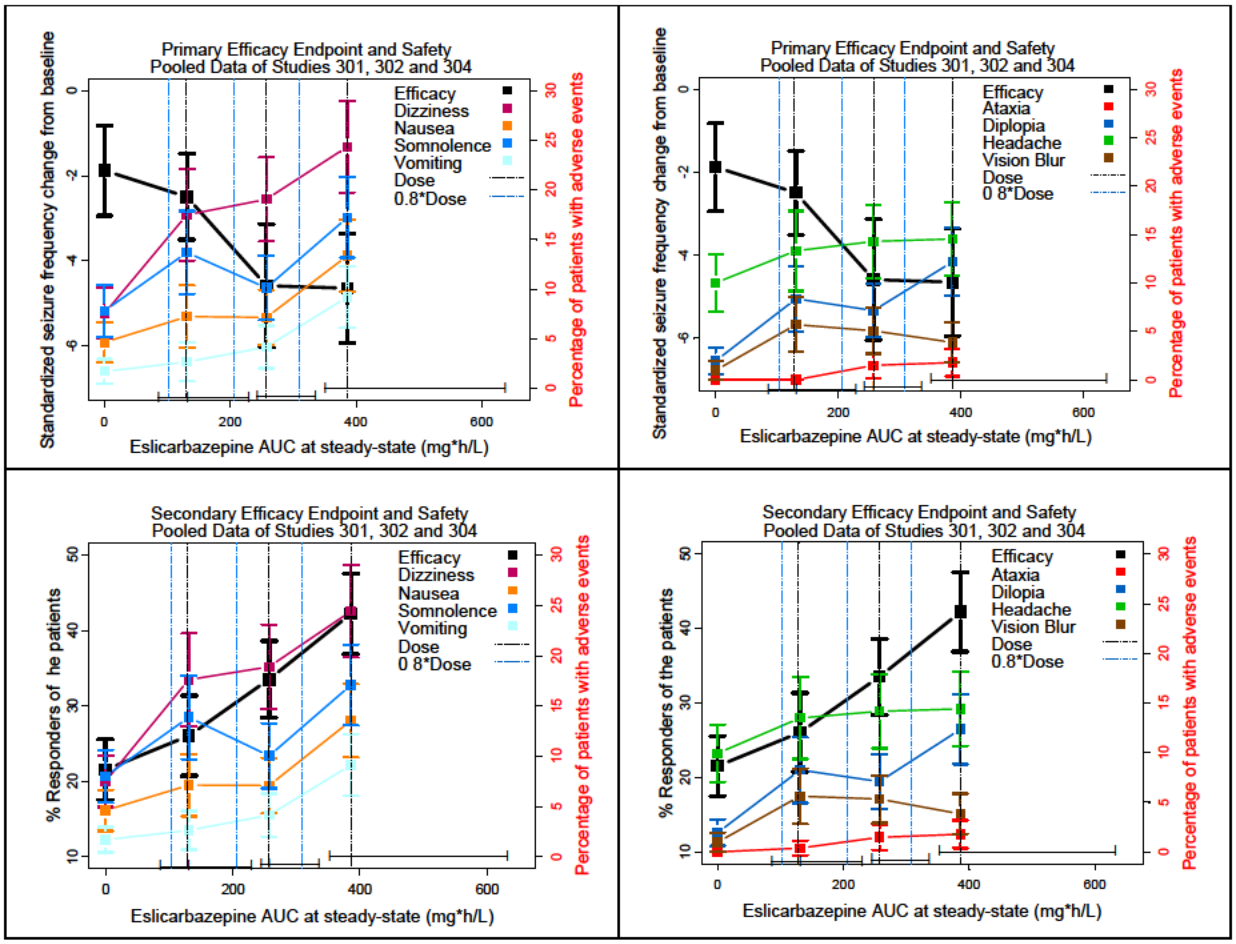
2.1.8 What dose of eslicarbazepine acetate, given once daily, is appropriate as an adjunctive therapy in the treatment of partial-onset seizures in adults?

Eslicarbazepine acetate (ESL) 800-1200 mg once daily oral dose (QD) is efficacious as an adjunctive therapy in the treatment of partial-onset seizures in adult patients based on pooled data of three Phase III studies BIA-2093-301, BIA-2093-302 and BIA-2093-304 (abbreviated as Study 301, 302 and 304 in this report, respectively). The efficacy of ESL 400 mg QD is not established in the Phase III studies.

- Primary efficacy (standard seizure frequency change from baseline over a 12-week maintenance period preceded by a 2-week titration period) increased with ESL exposure across 400-1200 mg QD range (refer to the top two panels of Figure 1).
- Primary efficacy of ESL 800 mg and 1200 mg QD differentiated from placebo while efficacy of 400 mg QD was similar to placebo (refer to the top two panels of Figure 1).
- Secondary efficacy (responder rate of the patients) increased with ESL exposure across 400-1200 mg QD range (bottom two panels of Figure 1). A responder is a patient with seizure frequency reduced at least 50% from baseline due to the treatment over a 12-week maintenance period preceded by a 2-week titration period.
- Secondary efficacy of ESL 800 mg and 1200 mg QD differentiated from placebo while efficacy of 400 mg QD was similar to placebo (bottom two panels of Figure 1).
- Higher ESL exposure resulted in higher adverse event rates; the safety profiles of ESL 800 and 1200 mg QD were acceptable in general (Figure 1).

In summary, ESL 800-1200 mg QD is efficacious as an adjunctive therapy in the treatment of partial-onset seizures in adult patients with acceptable safety profiles.

Figure 1. Change from baseline seizure frequency and percentage of patients with adverse events versus exposure profiles of pooled data of Phase III Studies BIA-2093-301, BIA-2093-302 and BIA-2093-304. Shown are the mean values and the 95% confidence intervals. Vertical dotted lines in black represent median exposures of 400, 800 and 1200 mg eslicarbazepine once daily dose



2.1.9 Is there any significant covariate that influences ESL PK and warrants ESL dose adjustment based on population PK analysis?

Yes, two conditions need dose adjustment based on sponsor's population PK analysis:

- The ESL dose should be increased by 50% when the patient co-administers ESL with phenobarbital or phenobarbital-like metabolic inducers (phenytoin and primidone). Co-administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin and primidone) reduced steady-state ESL exposure (AUC_{ss}) by 33.8% (refer to sponsor's population PK Report No. COG002419-2012-ESLIPK Page 9).
- The ESL dose should be increased by 50% when the patient co-administers ESL with carbamazepine. Co-administration of carbamazepine reduced ESL AUC_{ss} by 25.1-46.8% (refer to sponsor's population PK Report No. COG002419-2012-ESLIPK Page 9).

In summary, ESL dose should be increased by 50% when the patient co-administers ESL with carbamazepine; phenobarbital, phenytoin and primidone. The sponsor did not identify any other covariates that warrant a dose adjustment based on the population PK analysis of ESL data from 11 Phase I studies and 3 Phase III studies.

2.1.10 Does ESL influence any anti-epilepsy drug's (AED's) PK that warrants the AED's dose adjustment based on population PK analysis?

No. Sponsor's population PK analysis suggests that no dose adjustment is needed for carbamazepine, valproate, levetiracetam, phenobarbital, phenytoin, or gabapentin when coadministered with ESL. There is no information on other AEDs in the population PK report.

Based on pooled data of Studies 301, 302 and 304, the sponsor developed population PK models for these 6 AEDs (carbamazepine, valproate, levetiracetam, phenobarbital, phenytoin, and gabapentin) and studied exposure interaction between ESL and each AED separately. ESL does not affect any of these 6 AED's exposure that warrants a dose adjustment based on the analysis results (refer to sponsor's population PK Report COG002419-2012-AEDPK Page 9-10).

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 1: INDIVIDUAL STUDY REVIEW

BA/BE Studies

Study **BIA-2093-130**	Comparative bioavailability study of two different sources of eslicarbazepine acetate in healthy subjects
Principal Investigator	Didier CHASSARD, MD
Study Center	Biotrial Rennes, 7-9, rue Jean-Louis Bertrand, 35000 Rennes, France Biotrial Paris, 1, rue Charles Drot, 92500 Rueil-Malmaison, France
Study Period	10/4/10 – 11/15/10
Study Objective	To demonstrate the bioequivalence (BE) between two active product ingredient (API) sources [current API source – marketed formulation (MF) versus new API source – to-be-marketed (TBM)] of eslicarbazepine acetate (ESL) at two dosage strength (400 mg and 800 mg) after a single oral dose administration under fasting conditions in healthy male and female subjects: • Formulation A (*Test*): An oral formulation containing 400 mg or 800 mg of ESL tablet (new API source – TBM). • Formulation B (*Reference*): Zebinix® oral formulation containing 400 mg or 800 mg of ESL tablet (current API source – MF). *The sponsor brought on board a new active pharmaceutical ingredient (API) source. The tablets manufactured with it* (b) (4) *those manufactured with the current API. Therefore, a formal bioavailability/ bioequivalence (BA/BE) study had to be performed to prove that both sources give rise to equivalent API.*
Study Design and Dose Administration	This was a phase I, two-center, open-label, randomized, gender-balanced, single-dose, laboratory blinded, two-period, two-sequence, crossover study in 2 groups of 20 healthy male and female subjects. The study consisted in 2 periods separated by a wash-out of at least 7 days between doses. **Dosage strength 400 mg** (performed in Rennes): in Group 1, subjects randomly received on periods 1 and 2, either a single 400 mg tablet of ESL (MF), or a single 400 mg tablet of ESL (TBM); **Dosage strength 800 mg** (performed in Paris): in Group 2, subjects randomly received on period 1 and period 2, either a single 800 mg tablet of ESL (MF), or a single 800 mg dose of ESL (TBM). Formulations were orally given with 240 mL of water in the morning after a 10-hour overnight fast in each period. Subjects remained fasted for at least 4 hours after dosing.
Study Population	N= 40 healthy subjects (20 subjects/group). 38 subjects completed the study. 20 subjects (11M/9F) were in the study evaluating the 400 mg tablet; 18 subjects (10M/8F) were in the study evaluating the 800 mg tablet. Age: 21-54 (35.7) years Gender: 21M/19F Race: 3 Black, 34 Caucasian, 3 others.
Investigational Product	**Name** / **Formulation** / **Dose** / **Mode of administration** / **Batch number** ESL (TBM) / Tablet / 400 mg / oral / CCBG ESL (TBM) / Tablet / 800 mg / oral / CCBH ESL (MF) Zebinix® / Tablet / 400 mg / oral / PD269M-001 ESL (MF) Zebinix® / Tablet / 800 mg / oral / TXB
Sampling: Blood	For plasma ESL (BIA 2-093) and its active metabolite BIA 2-005

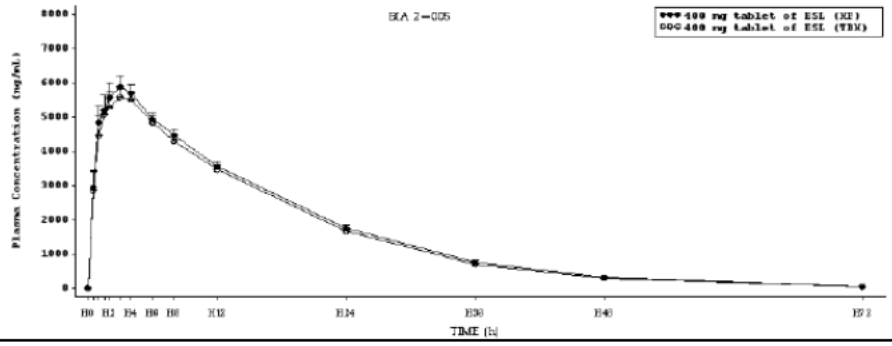
Reference ID: 3374277

<table>
<tr><td></td><td>(eslicarbazepine) concentrations (4 mL of blood for each time point): pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose on each dosing period.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Sample analysis was carried out at (b) (4) sing a validated method, which included solid phase extraction plasma sample preparation and liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS).

<table>
<tr><td></td><td>BIA 2-093 (parent)</td><td>BIA 2-005 (eslicarbazepine)</td></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>10-25000 ng/ml</td><td>10-25000 ng/ml</td></tr>
<tr><td>LLOQ</td><td>10 ng/ml</td><td>10 ng/ml</td></tr>
<tr><td>QCs</td><td>30, 1000, 20000 ng/ml</td><td>30, 1000, 20000 ng/ml</td></tr>
<tr><td>Inter-run precision</td><td>2.3 -7.9%</td><td>3.1 – 6.5%</td></tr>
<tr><td>Inter-run accuracy</td><td>92 - 105 %</td><td>94 – 104%</td></tr>
</table>

Quality control assay validation is acceptable.</td></tr>
<tr><td>PK Assessment</td><td>C_{max} , $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, T_{max}, and $T_{1/2}$</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td>ESL (parent) plasma concentrations were BLOQ in almost all sampling times (Subject 407 at 800 mg dosing group had measurable drug concentrations until 2 hours postdose in two periods).

Mean eslicarbazepine (BIA 2-005) plasma concentration-time profiles following a 400 mg and an 800 mg escarbazepine acetate (ESL) doses are presented below, respectively:

Figure 1: Mean (+SEM) BIA 2-005 plasma profile following single 400 mg administration of Zebinix® (MF, Reference) and ESL (TBM, Test) in 20 healthy subject Linear representation.

</td></tr>
</table>

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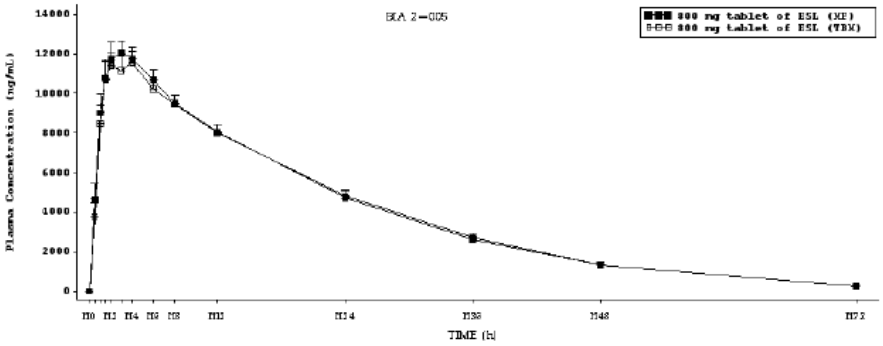
Reference ID: 3374277

Figure 2: Mean (+SEM) BIA 2-005 plasma profile following single 800 mg administration of Zebinix® (MF, *Reference*) and ESL (TBM, *Test*) in 18 healthy subject Linear representation.



Eslicarbazepine pharmacokinetic parameters following a 400 mg and an 800 mg dosing are listed in the following table:

Table 6: BIA 2-005 single dose PK parameters after single 400 mg and 800 mg administration of Zebinix® (MF, *Reference*) and ESL (TBM, *Test*) in 20 and 18 healthy subjects, respectively.

Dose level	Parameter (unit)		*Reference*	*Test*
400 mg (n=20)	C_{max} (ng/ml)	Mean* ± sd	6461 ± 1346	6547 ± 1524
		CV (%)	21	23
	t_{max}	Median (min-max)	2.00 (0.50-6.00)	2.00 (0.50-6.00)
	AUC_{0-t} (ng.hr/ml)	Mean* ± sd	112568 ± 23011	108224 ± 23971
		CV (%)	20	22
	$AUC_{0-\infty}$ (ng.hr/ml)	Mean* ± sd	113419 ± 23254	109034 ± 24253
		CV (%)	21	22
	$t_{1/2}$ (h)	Mean* ± sd	9.60 ± 1.40	9.49 ± 1.52
		CV (%)	15	16
800 mg (n=18)	C_{max} (ng/ml)	Mean* ± sd	13183 ± 2564	12988 ± 2215
		CV (%)	19	17
	t_{max}	Median (min-max)	2.00 (1.00-4.02)	1.75 (1.00-6.00)
	AUC_{0-t} (ng.hr/ml)	Mean* ± sd	279035 ± 60183	278734 ± 61738
		CV (%)	22	22
	$AUC_{0-\infty}$ (ng.hr/ml)	Mean* ± sd	282926 ± 61000	283394 ± 63318
		CV (%)	22	22
	$t_{1/2}$ (h)	Mean* ± sd	12.1 ± 1.7	12.4 ±1.9
		CV (%)	14	16

*Arithmetic mean

The statistical analysis shows that the AUC and Cmax are within the 90% CI for eslicarbazepine between reference and tested tablets:

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	<table><tr><th>Dose level</th><th>Parameter (unit)</th><th>Treatment group</th><th>Geometric mean</th><th>Point estimate Ratio Test/Reference</th><th>90% Confidence Interval</th></tr><tr><td rowspan="6">400 mg</td><td rowspan="2">C_{max} (ng/ml)</td><td>Reference</td><td>6320</td><td rowspan="2">1.01</td><td rowspan="2">[0.94; 1.09]</td></tr><tr><td>Test</td><td>6391</td></tr><tr><td rowspan="2">AUC_{0-t} (ng.hr/ml)</td><td>Reference</td><td>110298</td><td rowspan="2">0.96</td><td rowspan="2">[0.94 ; 0.98]</td></tr><tr><td>Test</td><td>105853</td></tr><tr><td rowspan="2">$AUC_{0-\infty}$ (ng.hr/ml)</td><td>Reference</td><td>111129</td><td rowspan="2">0.96</td><td rowspan="2">[0.94 ; 0.98]</td></tr><tr><td>Test</td><td>106622</td></tr><tr><td rowspan="6">800 mg</td><td rowspan="2">C_{max} (ng/ml)</td><td>Reference</td><td>12950</td><td rowspan="2">1.00</td><td rowspan="2">[0.95; 1.05]</td></tr><tr><td>Test</td><td>12808</td></tr><tr><td rowspan="2">AUC_{0-t} (ng.hr/ml)</td><td>Reference</td><td>273474</td><td rowspan="2">1.00</td><td rowspan="2">[0.97 ; 1.03]</td></tr><tr><td>Test</td><td>272679</td></tr><tr><td rowspan="2">$AUC_{0-\infty}$ (ng.hr/ml)</td><td>Reference</td><td>277274</td><td rowspan="2">1.00</td><td rowspan="2">[0.97 ; 1.03]</td></tr><tr><td>Test</td><td>277084</td></tr></table>
Safety	There was no SAE or death in the study. The majority of TEAEs were considered of mild intensity. No TEAEs were reported in subjects receiving ESL 400 mg (MF); 2 TEAEs were reported by 5.0% of subjects (1/20) receiving ESL 400 mg (TBM); 5 TEAEs were reported by 20.0% subjects (4/20) receiving ESL 800 mg (MF); 6 TEAEs were reported by 22.2% (4/18) subjects receiving ESL 800 mg (TBM).
Conclusion	The oral formulations containing 400 mg or 800 mg of ESL of the new API source are bioequivalent to the current API source for both 400 mg and 800 mg of ESL (Zebinix®, market formulation), respectively.

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Study SEP093-155	A PK Comparison Study of Eslicarbazepine Acetate Administered Orally as Either Crushed or Intact Tablet in Healthy Male and Female Subjects.
Principal Investigator	Ralph A. Schutz, MD
Study Center	Quintiles Phase One Services 6700 West 115th Street Overland Park, KS 66211
Study Period	6/15/11 – 8/15/11 (First Subject First Visit – Last Subject Last Visit)
Primary Objective	To investigate and compare the relative bioavailability and bioequivalence of a crushed tablet and an intact tablet of eslicarbazepine acetate (800 mg) in healthy male and female subjects.
Study design and Dose Administration	This was a single-center, randomized, open-label, 2-period, cross-over, single-dose study of 800 mg eslicarbazepine acetate administered as a crushed versus an intact tablet in healthy male and female volunteers. Eligible subjects were randomized to 1 of the 2

<table>
<tr><td></td><td>following cross-over treatment sequences with a 1:1 allocation ratio (14 subjects per treatment sequence):
• Treatment A→B: Single oral dose 800 mg as a crushed tablet (treatment A) to single oral dose 800 mg as an intact tablet (treatment B) of eslicarbazepine acetate.
• Treatment B→A: Single oral dose 800 mg as an intact tablet (treatment B) to single oral dose 800 mg as a crushed tablet (treatment A) of eslicarbazepine acetate.
The total duration of the study was approximately 7 weeks, including an up to 21-day screening period, a 12-day treatment period (inclusive of an at least 5-day wash-out period between treatments), and a 10- to 14-day follow-up period. The study involved 4 clinic visits and approximately 10 days of in-clinic stay.
Whole tablets were dispensed from a bulk bottle and administered without changes. Crushed tablets were prepared by placing 1 eslicarbazepine acetate 800 mg tablet in a small poly bag and into the chamber of a clean “tablet crusher” device that was provided to the clinic by the sponsor. Following directions provided in the Pharmacists’ Instruction Manual, the tablet was crushed. The small poly bag containing the crushed tablet was removed from the crushing device, the crushing device was dry cleaned, if necessary, and the procedure was repeated using a clean poly bag to crush 1 x 800 mg tablet for the next subject, as needed for all subjects in that dosing period.
A single oral dose of 800 mg eslicarbazepine acetate administered as 1 x 800 mg tablet was to be taken in the morning (after a minimum 8-hour overnight fast) either as an intact tablet (immediately followed by 4 ounces of applesauce and 8 ounces of water in that order) or as a crushed tablet sprinkled on a 4-ounce container of applesauce (immediately followed by 8 ounces of water) according to the randomization schedule.</td></tr>
<tr><td>Study Population</td><td>N=28 healthy subjects (21M/7F), 27 completed the study. One subject (001-S059) received crushed tablet on Day 1, but was lost to follow-up and did not receive the intact tablet on Day 8. This subject has been included in PK summary presentations, but excluded from the PK analyses comparing treatments.
Age: 18-45 yr
Race: 19 Caucasian, 8 Black, 3 Asian, and 1 Native American.</td></tr>
<tr><td>Investigational Product</td><td>Product Description — Primary Lot / Batch #
Eslicarbazepine acetate 800 mg tablets — Sunovion Lot # DHKD
(white oblong tablets, engraved ESL 800 on one side and with a groove on the other side) — Packager Lot # 051I0511
(Open Label)</td></tr>
</table>

Reference ID: 3374277

<table>
<tr><td>Sampling: Blood</td><td>Predose, 30 minutes, and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours postdose on Days 1 and 8.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Sample analysis was performed at [redacted] (b) (4) between 08/01/11 and 10/31/11.

<table>
<tr><td></td><td>Eslicarbazepine</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>50 - 25000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>50</td></tr>
<tr><td>QCs (ng/ml)</td><td>150, 4500, 20000</td></tr>
<tr><td>Inter-assay precision</td><td>% CV: 3 – 7.7 %</td></tr>
<tr><td>Inter-assay accuracy</td><td>% Normal: 99 - 107</td></tr>
</table>

<table>
<tr><td></td><td>Eslicarbazepine Acetate</td><td>(R)- licarbazepine</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>50 - 1000</td><td>50 - 25000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>50</td><td>50</td></tr>
<tr><td>QCs (ng/ml)</td><td>50, 150, 450, 800</td><td>150, 4500, 20000</td></tr>
<tr><td>Inter-assay precision</td><td>% CV: 2.5 – 9.7 %</td><td>% CV: 2.7 - 12.1%</td></tr>
<tr><td>Inter-assay accuracy</td><td>% Normal: 100 - 104</td><td>% Normal: 99 - 107</td></tr>
</table>

Quality control assay validation is acceptable</td></tr>
<tr><td>PK Assessment</td><td>The primary analyses compared Cmax and AUC0-∞ of eslicarbazepine between 2 dosage forms (crushed tablet versus intact tablet; intact tablet was the reference). A nonparametric analysis was used to assess the difference in tmax between the 2 treatments.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, C-SSRS item responses and AEs.</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td><u>Eslicarbazepine:</u>
Mean eslicarbazepine plasma concentration-time profile by treatment following an 800 mg escarbazepine acetate dose (PK population):</td></tr>
</table>

Reference ID: 3374277

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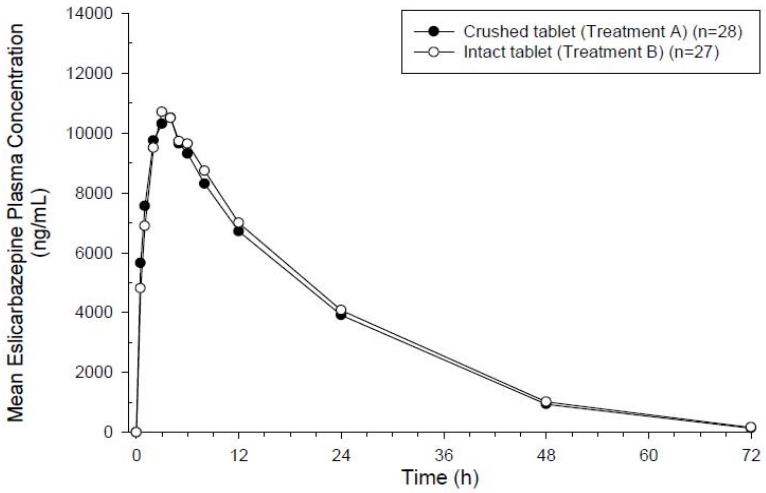


Note: mean values after 72 hours were BLQ for both treatments

Eslicarbazepine pharmacokinetic parameters are given in the following Table:

Parameter	Crushed Tablet (Treatment A) (N=28)	Intact Tablet (Treatment B) (N=27)
C_{max} (ng/mL)	11699 (2843)	11522 (2967)
t_{max} (hr)	3.00 (1.00, 5.00)	3.00 (0.48, 6.00)
$AUC_{0-\infty}$ (ng·hr/mL)	225214 (44497)	234000 (46600)
AUC_{0-last} (ng·hr/mL)	222393 (44708)	231222 (46557)
$t_{1/2}$ (hr)	10.20 (0.98)	10.31 (1.26)
CL/F (L/hr)	3.18 (0.71)	3.06 (0.66)
Vz/F (L)	46.8 (11.7)	45.3 (10.8)

Abbreviations: hr = hour; SD = standard deviation.
Note: n = 28 for each parameter for treatment A and n = 27 for each parameter for treatment B.
Note: Parameters are reported as mean (SD), except for t_{max}, which is reported as median (minimum, maximum).

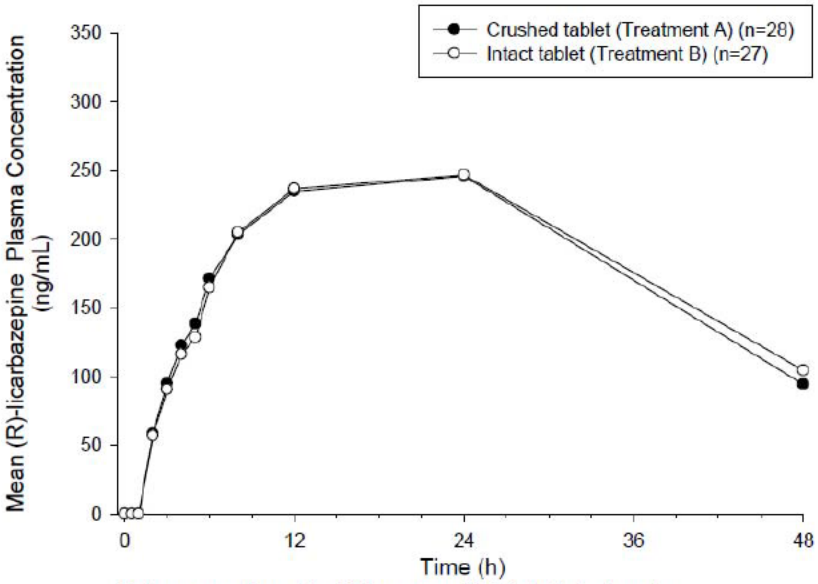
The statistical analysis shows that the AUC and Cmax are within the 90% CI for eslicarbazepine when administered an intact table or crushed tablet of 800 mg.

Parameter	Treatment	n[a]	Geometric LS mean	Comparison of Crushed versus Intact Tablet		
				Geometric LS mean Ratio[b]	90% Confidence Interval[b]	
Primary Analyses						
C_{max} (ng/mL)	Crushed Tablet	27	11387.0	102.63	97.07	108.51
	Intact Tablet	27	11095.1			
$AUC_{0-\infty}$ (ng·hr/mL)	Crushed Tablet	27	221393.8	96.72	94.36	99.13
	Intact Tablet	27	228911.9			
Secondary Analysis						
AUC_{0-last} (ng·hr/mL)	Crushed Tablet	27	218613.2	96.69	94.24	99.21
	Intact Tablet	27	226095.5			

Abbreviations: hr = hour; LS = least squares.
[a] Only subjects in the PK population who had evaluable data from both treatments (crushed and intact) were included in this analysis.
[b] Derived using a linear mixed-effect model with the natural-log transformed PK parameter as the dependent variable; treatment, treatment sequence, and treatment period as fixed effects; and subject nested within treatment sequence as a random effect. Crushed tablet was the test and intact tablet was the reference.

For both the crushed and intact tablet, the median tmax was 3.00 hours; the difference between treatments was not statistically significant (p= 0.5209). The mean eslicarbazepine t1/2 was similar whether the tablet was crushed or taken intact (10.20 and 10.31 hours for crushed and intact tablets, respectively).

Reference ID: 3374277

	Eslicarbazepine acetate: Eslicarbazepine acetate plasma concentration measurements were BLOQ for all subjects at all time points for both treatments. **(R)-Licarbazepine:** Mean (R)-licarbazepine plasma concentration-time profile by treatment following an 800 mg escarbazepine acetate dose (PK population):  Note: mean values after 48 hours were BLQ for both treatments
Safety	No death or SAEs was reported. 27 treatment emergent adverse events (TEAEs) were observed in 28 subjects. There was a similar incidence of TEAEs across treatments (28.6% of subjects reported a total of 16 TEAEs for crushed tablet and 29.6% of subjects reported a total of 11 TEAEs for intact tablet).
Conclusion	The PK of the 800 mg tablet of eslicarbazepine acetate is not significantly altered by crushing.

DDI Studies in Healthy Subjects

Study **BIA-2093-129**	Pharmacokinetic interaction study between eslicarbazepine acetate and carbamazepine in healthy subjects
Principal Investigator	Dr Nicolas FAUCHOUX
Study Center	Biotrial, 7-9, rue Jean-Louis Bertrand, F- 35000 Rennes, France
Study Period	7/10/09 – 11/13/09
Primary Study Objective	To assess the interaction between eslicarbazepine acetate (ESL) and carbamazepine (CBZ) in healthy subjects.
Study Design and	Open-label study in two parallel groups of 20 healthy subjects each.

<table>
<tr><td>Dose Administration</td><td>Group A assessed the effect of CBZ on ESL pharmacokinetics, and Group B assessed the effect of ESL on CBZ pharmacokinetics.
<table>
<tr><th>Group</th><th>Treatment</th><th>Dose (mg)</th><th>Day</th><th>Mode of administration</th><th>Fasting conditions</th></tr>
<tr><td>A</td><td>ESL</td><td>800 mg</td><td>D1 to D35</td><td>q.d. in the morning</td><td>After an overnight fasting for D7 and D35</td></tr>
<tr><td></td><td>CBZ (Tegretol® CR)</td><td>200 mg
400 mg</td><td>D8 to D14
D15 to D21
D22 to D35</td><td>q.d. in the morning
q.d. in the morning
b.i.d. in the morning and evening</td><td>no
no
no</td></tr>
<tr><td>B</td><td>ESL</td><td>800 mg</td><td>D29 to D35</td><td>q.d. in the morning</td><td>After an overnight fasting on D35</td></tr>
<tr><td></td><td>CBZ (Tegretol® CR)</td><td>200 mg
400 mg</td><td>D1 to D7
D8 to D14
D15 to D35</td><td>q.d. in the morning
q.d. in the morning
b.i.d. in the morning and evening</td><td>no
no
After an overnight fasting for D28 and D35</td></tr>
</table></td></tr>
<tr><td>Study Population</td><td>N= 40 healthy subjects (20 subjects/group). 38 subjects completed the study (18 subjects in Group A and 20 subjects in Group B).
Age: 18-46 years
Gender: 26M/17F
Race: no information.</td></tr>
<tr><td>Investigational Product</td><td>
<table>
<tr><th>Name</th><th>Formulation</th><th>Strength (mg)</th><th>Batch number</th><th>Expiry date</th></tr>
<tr><td>ESL</td><td>Tablet</td><td>800 mg</td><td>080481</td><td>JUL-2011</td></tr>
<tr><td>CBZ Tégrétol® LP</td><td>Divisible tablet</td><td>200 mg</td><td>T0582</td><td>FEB-2012</td></tr>
<tr><td></td><td></td><td>400 mg</td><td>T0882</td><td>APR-2012</td></tr>
</table></td></tr>
<tr><td>Sampling: Blood</td><td>In Group A, blood samples for eslicarbazepine and R-licarbazepine plasma assay were taken before the ESL dose on Day 1, 5 and 6, and at the following time-points on Days 7 and 35: within 5 minutes prior to dosing, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 h after ESL administration. On Days 8, 15, 21, 28 and 35, blood samples for the assay of carbamazepine and carbamazepine-epoxide were taken before the CBZ morning dose.
In Group B, blood samples for carbamazepine and carbamazepine-epoxide plasma assay were taken before the CBZ dose on Day 1, 8, 15, 21 and 25, and at the following time-points on Days 28 and 35: within 5 minutes prior to dosing, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9 and 12 h after CBZ administration. On Days 29, 33, 34 and 35, blood samples for the assay of eslicarbazepine and R-licarbazepine were taken before the ESL dose.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>ESL: Plasma levels of ESL and R-licarbazepine were evaluated using a validated method, which included solid phase extraction plasma sample preparation and HPLC separation with mass spectrometry (LC-MS/MS).
CBZ: Plasma level of CBZ and Carbamazepine 10,11-Epoxide were determined using LC-MS-MS, LLOQ of 50 ng/mL for CBZ, LLOQ of 5 ng/mL for Carbamazepine 10,11- Epoxide.
These samples were analyzed by
• Eslicarbazepine: (b) (4)</td></tr>
</table>

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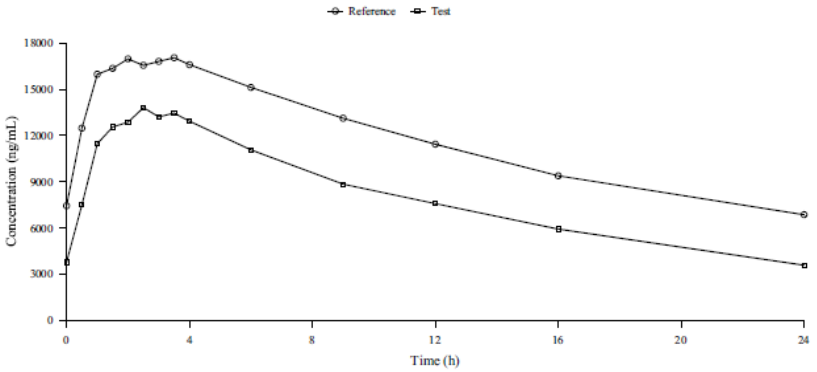
Reference ID: 3374277

<table>
<tr><td></td><td>
Carbamazepine: [redacted] (b) (4)
<table>
<tr><th></th><th>BIA 2-194 (eslicarbazepine)</th><th>CBZ</th><th>CBZ 10,11-Epoxide</th></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>50-25000</td><td>49.8 – 9782.4</td><td>5.1 – 2011.8</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>50</td><td>49.8</td><td>5.1</td></tr>
<tr><td>QCs (ng/ml)</td><td>50, 150, 4500, 20000.</td><td>149.7, 399.8, 3962, 7846.3.</td><td>15.6, 83, 823, 1630.</td></tr>
<tr><td>Inter-run precision</td><td>3 -7.7%</td><td>10.7 – 11.3%</td><td>7.1 – 12.1%</td></tr>
<tr><td>Inter-run accuracy</td><td>98.7 – 105.5 %</td><td>98 – 107.6%</td><td>102.2 – 110.1%</td></tr>
</table>
Quality control assay validation is acceptable.
</td></tr>
<tr><td>PK Assessment</td><td>Group A: For the evaluation of the effect of CBZ on the ESL PK, $AUC_{0-\tau}$ and Cmax of eslicarbazepine and R-licarbazepine were the primary variables.
The sponsor only evaluated the effect of CBZ on PK of eslicarbazepine because a technical problem was detected on quantification of R-licarbazepine [redacted] (b) (4)

Group B: For the evaluation of the effect of ESL on the CBZ pharmacokinetics, $AUC_{0-\tau}$ and Cmax of carbamazepine and carbamazepine-epoxide were the primary variables.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td>Group A: the effect of CBZ on ESL PK:
Mean eslicarbazepine plasma concentration-time profiles following 800 mg escarbazepine acetate (ESL) QD alone on Day7 and concomitantly with CBZ 400 mg BID on Day 35 are presented below:</td></tr>
</table>

Reference ID: 3374277

Figure 6: Mean plasma eslicarbazepine concentration-time profile following once-daily oral administration of ESL 800 mg alone (Day 7; *Reference*) and concomitantly with twice-daily oral CBZ 400 mg (Day 35; *Test*)



Eslicarbazepine pharmacokinetic parameters following 800 mg escarbazepine acetate (ESL) QD alone on Day7 and concomitantly with CBZ 400 mg BID on Day 35 are listed in the following tables, respectively:

Table 6: Mean plasma pharmacokinetic parameters of eslicarbazepine at Day 7 (*Reference*) following once-daily oral administration of ESL 800 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	18	18	18	18	18	18
Gmean	18601	1.72	276836	276836	0.0439	15.8
Amean	18821	1.94	279605	279605	0.0445	16.0
SD	3164	0.97	43062	43062	0.0072	2.72
CV (%)	16.8	49.8	15.4	15.4	16.2	17.0
Median	18379	2.00	269112	269112	0.0443	15.7
Minimum	14589	0.50	226740	226740	0.0312	12.2
Maximum	28843	4.00	415213	415213	0.0569	22.2

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean;
SD = Standard deviation; CV = Coefficient of variation

Table 7: Mean plasma pharmacokinetic parameters of eslicarbazepine at Day 35 (*Test*) following once-daily oral administration of ESL 800 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	18	18	18	18	18	18
Gmean	14591	1.89	188648	188648	0.0633	11.0
Amean	14691	2.17	190012	190012	0.0642	11.1
SD	1800	1.07	23897	23897	0.0111	2.06
CV (%)	12.3	49.4	12.6	12.6	17.2	18.6
Median	14361	2.25	186626	186626	0.0643	10.8
Minimum	11950	0.50	159623	159623	0.0431	8.32
Maximum	19476	4.00	249813	249813	0.0833	16.1

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean;
SD = Standard deviation; CV = Coefficient of variation

AUC and Cmax of eslicarbazepine decreased by 32% and 22% following the concomitant administration with CBZ compared to the administration alone, respectively.
The statistical analysis is shown below:

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Reference ID: 3374277

Table 8: Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of C_{max} and $AUC_{0-\tau}$ for eslicarbazepine following once-daily oral administration of ESL 800 mg alone (Day 7; *Reference*) and concomitantly with twice-daily oral CBZ 400 mg (Day 35; *Test*)

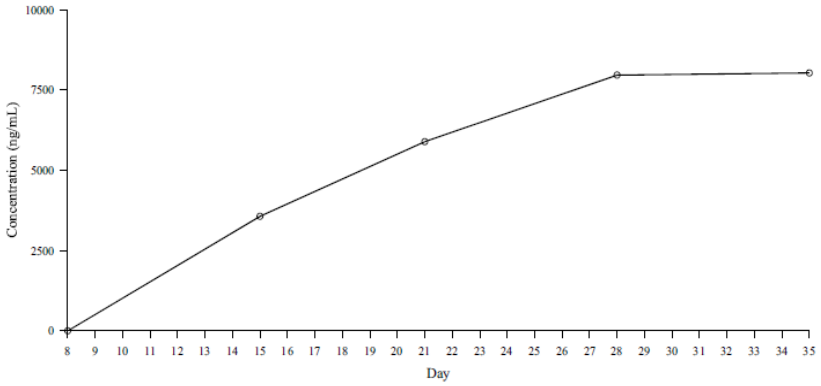
		Test/Reference
C_{max} (ng/mL)	PE	78.44
	90% CI	72.61; 84.74
$AUC_{0-\tau}$ (ng.h/mL)	PE	68.14
	90% CI	63.25; 73.42

Point Estimate; CI = Confidence Interval.

No differences on t_{max} were found.

The mean trough concentration-time profile of CBZ is presented below:

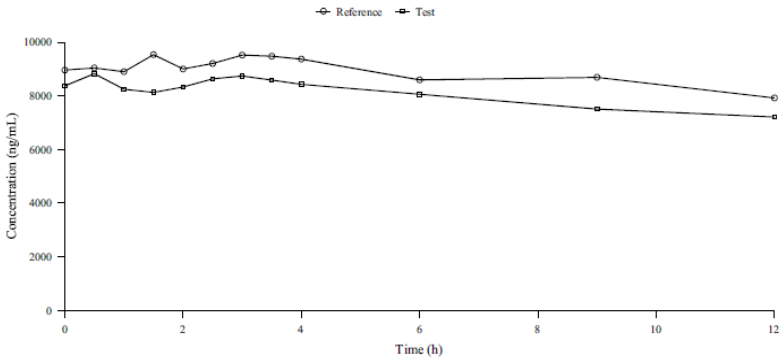
Figure 1: Mean trough plasma CBZ concentration-time profile at Days 8, 15, 21, 28 and 35 following oral administration of CBZ accordingly to the dosing schedule (D8 to D14 200 mg q.d.; D15 to D21 400 mg; D22 to D35 400 mg b.i.d.)



Group B: the effect of ESL on CBZ pharmacokinetics:

The mean plasma CBZ concentration-time profiles following CBZ alone and combination of CBZ and ESL is shown below:

Figure 14: Mean plasma CBZ concentration-time profile following twice-daily oral administration of CBZ 400 mg alone (Day 28; *Reference*) and concomitantly with once-daily oral ESL 800 mg (Day 35; *Test*)



The mean PK parameters of CBZ following oral administration of CBZ alone and combination of CBZ and ESL are presented below,

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respectively:

Table 9: Mean plasma pharmacokinetic parameters of CBZ at Day 28 (*Reference*) following twice-daily oral administration of CBZ 400 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	20	20	20	20	16	16
Gmean	10414	2.70	104494	104494	0.0237	29.2
Amean	10583	3.18	105745	105745	0.0254	31.3
SD	1896	1.85	16344	16344	0.0097	11.8
CV (%)	17.9	58.3	15.5	15.5	38.3	37.8
Median	10173	3.25	106255	106255	0.0245	28.4
Minimum	6436	0.50	68063	68063	0.0130	15.7
Maximum	13717	9.00	138940	138940	0.0443	53.2

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean;
Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 10: Mean plasma pharmacokinetic parameters of CBZ at Day 35 (*Test*) following twice-daily oral administration of CBZ 400 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	20	20	20	20	17	17
Gmean	9719	1.73	94394	94394	0.0274	25.3
Amean	9918	2.23	95878	95878	0.0299	27.5
SD	2019	1.44	17230	17230	0.0136	11.9
CV (%)	20.4	64.6	18.0	18.0	45.5	43.3
Median	10050	2.50	93863	93863	0.0277	25.0
Minimum	6656	0.50	66516	66516	0.0120	10.1
Maximum	12890	6.00	129842	129842	0.0686	57.8

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean;
Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK profiles of CBZ are shown similar between oral administration of CBZ alone and combination of CBZ and ESL.

The statistical analysis is shown below:

Table 13: Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of C_{max} and $AUC_{0-\tau}$ for CBZ following twice-daily oral administration of CBZ 400 mg alone (Day 28; *Reference*) and concomitantly with once-daily oral ESL 800 mg (Day 35; *Test*)

		Test/Reference
C_{max} (ng/mL)	PE	93.33
	90% CI	83.99; 103.71
$AUC_{0-\tau}$ (ng.h/mL)	PE	90.33
	90% CI	82.42; 99.01

PE = Point Estimate; CI = Confidence Interval.
No differences on t_{max} were found.

CBZ metabolite, CBZE concentration-time profiles following oral administration of CBZ alone and combination of CBZ and ESL are shown below:

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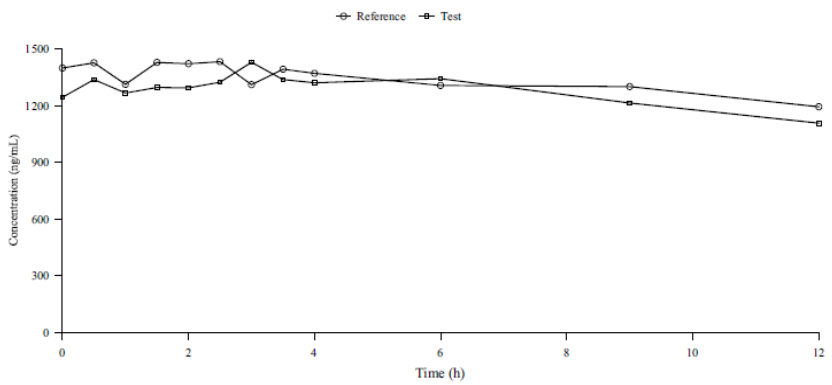
Figure 15: Mean plasma CBZE concentration-time profile following twice-daily oral administration of CBZ 400 mg alone (Day 28; *Reference*) and concomitantly with once-daily oral ESL 800 mg (Day 35; *Test*)



PK parameters of CBZE following oral administration of CBZ alone and combination of CBZ and ESL are shown below:

Table 11: Mean plasma pharmacokinetic parameters of CBZE at Day 28 (*Reference*) following twice-daily oral administration of CBZ 400 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	20	20	20	20	14	14
Gmean	1562	1.85	15322	15322	0.0270	25.7
Amean	1630	2.58	15889	15889	0.0284	27.3
SD	429	2.09	3857	3857	0.0081	11.2
CV (%)	26.3	81.2	24.3	24.3	28.6	41.2
Median	1574	2.50	15976	15976	0.0310	22.4
Minimum	515	0.50	5421	5421	0.0122	18.0
Maximum	2280	9.00	23045	23045	0.0384	56.8

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean;
Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 12: Mean plasma pharmacokinetic parameters of CBZE at Day 35 (*Test*) following twice-daily oral administration of CBZ 400 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	λ_z (h)	$t_{1/2}^{\#}$ (h)
N	20	20	20	20	17	17
Gmean	1560	2.15	14953	14953	0.0386	18.0
Amean	1594	2.75	15267	15267	0.0423	20.3
SD	332	1.73	3121	3121	0.0169	12.2
CV (%)	20.8	62.8	20.4	20.4	40.0	60.3
Median	1628	3.00	16152	16152	0.0414	16.7
Minimum	1008	0.50	10356	10356	0.0115	10.1
Maximum	2194	6.00	21708	21708	0.0684	60.4

# = Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects;
N = Number of subjects; Gmean = Geometric mean;
Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK profiles of CBZE are also shown similar between oral administration of CBZ alone and combination of CBZ and ESL. The statistical analysis is shown below:

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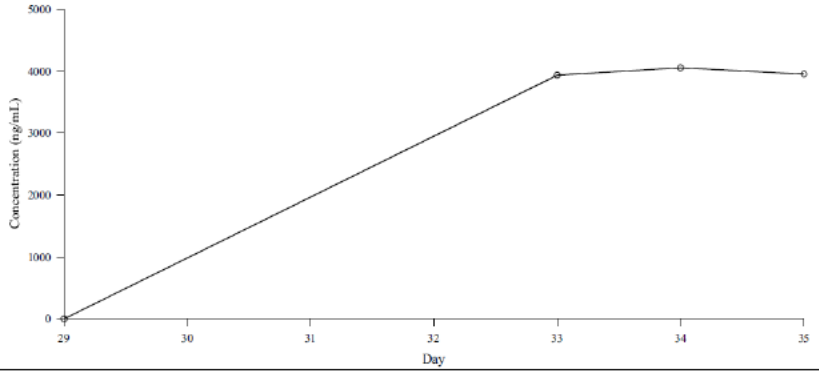
	Table 14: Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of C_{max} and $AUC_{0-\tau}$ for CBZE following twice-daily oral administration of CBZ 400 mg alone (Day 28; *Reference*) and concomitantly with once-daily oral ESL 800 mg (Day 35; *Test*) PE = Point Estimate; CI = Confidence Interval. No differences on t_{max} were found. The mean trough concentration-time profile of ESL is presented below: **Figure 7: Mean trough plasma eslicarbazepine concentration-time profile at Days 29, 33, 34 and 35 following once-daily oral administration of ESL 800 mg**
Safety	There was no SAE or death in the study. No relevant change of incidence of TEAEs was observed during concomitant administration of CBZ and ESL compared to during administration of ESL alone or CBZ alone. However TEAEs in the nervous system disorders tended to be more frequent when ESL was coadministered with CBZ than when CBZ was administered alone. Most TEAEs were mild to moderate in intensity.
Conclusion	AUC and Cmax of eslicarbazepine decreased by 32% and 22% following the concomitant administration with CBZ at 400 mg BID compared to the administration of ESL alone, respectively. Concomitant oral once-daily administration of ESL 800 mg with CBZ did not affect the carbamazepine and carbamazepine-epoxide kinetic profile.

	Test/Reference
C_{max} (ng/mL) PE	99.89
90% CI	86.07; 115.93
$AUC_{0-\tau}$ (ng.h/mL) PE	97.59
90% CI	84.94; 112.14



Study **BIA-2093-124**	Effect of repeated administration of eslicarbazepine acetate on the pharmacokinetics of simvastatin in healthy subjects.
Principal	Dr. Marie-Claude Homery, MD

<table>
<tr><td>Investigator</td><td></td></tr>
<tr><td>Study Center</td><td>Biotrial, 7-9, rue Jean-Louis Bertrand, F- 35000 Rennes, France</td></tr>
<tr><td>Study Period</td><td>6/9/09 – 11/25/09</td></tr>
<tr><td>Primary Study Objective</td><td>To investigate whether multiple-dose administration of eslicarbazepine acetate (ESL) 800 mg once-daily affects the pharmacokinetics of simvastatin (S), a substrate of CYP3A4.
ESL appeared to have a slight effect on the activity of CYP3A4 in vitro human liver microsomes, EMEA requested the investigation of the inducing effects of ESL on CYP3A4 in vivo conditions.
Simvastatin, a known CYP3A4 substrate, was chosen for this study.</td></tr>
<tr><td>Study Design and Dose Administration</td><td>Single center, two-way cross-over, randomized, open-label study in 24 healthy volunteers. The 2-period cross-over phase was constituted by:
- a single-dose of 80 mg simvastatin (S period)
- a 14-day treatment with ESL 800 mg q.d., in which a single-dose of 80 mg simvastatin was co-administered with the dose of ESL administered on D14 (ESL+S period).
Both periods were separated by an interval of at least 3 weeks (wash-out).
Simvastatin 80 mg was administered as two 40 mg tablets in fasting conditions (8 hours), once on its own and once following the 14-day administration of ESL 800 mg once daily.</td></tr>
<tr><td>Study Population</td><td>30 subjects randomized in the study; 24 healthy subjects completed the study with available plasma concentrations.
<u>Age:</u> 20-45 years
<u>Gender</u>: 14M/16F
<u>Race</u>: no information.</td></tr>
<tr><td>Investigational Product</td><td>
<table>
<tr><th>Name</th><th>Formulation</th><th>Strength (mg)</th><th>Batch number</th><th>Expiry date</th></tr>
<tr><td>Eslicarbazepine acetate</td><td>Tablet</td><td>800 mg</td><td>080481</td><td>July 2011</td></tr>
<tr><td>Simvastatin Zocor®</td><td>Film-coated tablet</td><td>40 mg</td><td>NK30340</td><td>November 2010</td></tr>
</table>
</td></tr>
<tr><td>Sampling: Blood</td><td>On Days 1, 4, 6, 10, 12 and 14 of the ESL+S period, blood samples (4 mL) for the assay of eslicarbazepine (ESL main active metabolite) were taken pre-dose ($_3$ trough $_4$ levels).
On the S period and ESL+S period, blood samples (10 mL) for the assay of simvastatin and simvastatin-hydroxyacid were taken at the following times in relation to the simvastatin dose: pre-dose (2 samples), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h post-dose.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma levels of simvastatin and simvastatin β-hydroxyacid and ESL were evaluated using a validated method, which includes solid phase extraction plasma sample preparation and HPLC separation with mass spectrometry (LC-MS/MS).
These samples were analyzed by (b) (4)

<table>
<tr><td></td><td>Simvastatin</td><td>Simvastatin β-hydroxyacid</td><td>BIA 2-194 (eslicarbazepin</td></tr>
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Reference ID: 3374277

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<tr><td></td><td>
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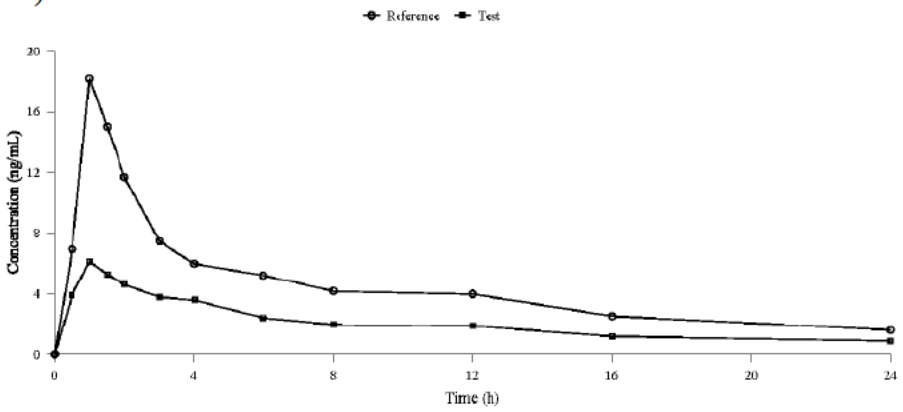
<tr><td></td><td></td><td></td><td>e)</td></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>0.1-50</td><td>0.1 - 20</td><td>50-25000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>0.1</td><td>0.1</td><td>50</td></tr>
<tr><td>QCs (ng/ml)</td><td>0.1, 0.3, 5, 40.</td><td>0.1, 0.3, 3, 16.</td><td>50, 150, 4500, 20000.</td></tr>
<tr><td>Inter-run precision</td><td>2 -9.5%</td><td>2.9 – 14.7%</td><td>3 – 7.7%</td></tr>
<tr><td>Inter-run accuracy</td><td>94.9 – 102.7 %</td><td>97 – 101.9%</td><td>98.7 – 107.2%</td></tr>
</table>

Quality control assay validation is acceptable.</td></tr>
<tr><td>PK Assessment</td><td>The following pharmacokinetic parameters for simvastatin and simvastatin β-hydroxyacid were derived, where appropriate, from the individual plasma concentration-time profiles: Cmax, tmax, AUC from time zero to the last sampling time at which concentrations were at or above the limit of quantification (AUC0-t), AUC from time zero to infinity (AUC0-∞), calculated by the linear trapezoidal rule, apparent terminal rate constant calculated by log-linear regression of the terminal segment of the concentration versus time curve (λz), apparent terminal half-life (t1/2) calculated from ln 2/λz. Other pharmacokinetic parameters could be calculated, if considered appropriate and justified at the time of the PK analysis.
The eslicarbazepine steady-state condition was assumed to be reached on the basis of visual observation of the pre-dose ($_3$ trough$_4$) values.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td><u>Simvastatin and simvastatin β-hydroxyacid</u>:
Mean plasma simvastatin concentration-time profile following single oral administration of SIM 80 mg alone (D1: Reference) and concomitantly with once daily oral administration of ESL 800 mg (D14 Test) is shown below:
 

Mean plasma simvastatin β-hydroxyacid concentration-time profile</td></tr>
</table>

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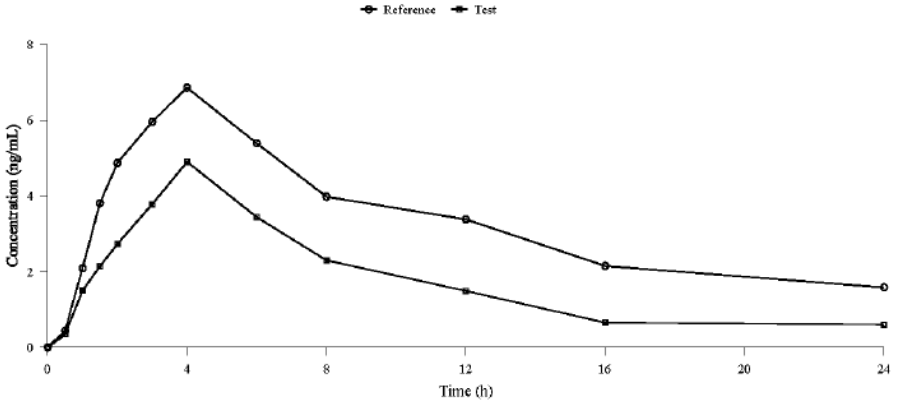
following single oral administration of SIM 80 mg alone (D1: Refrence) and concomitantly with once daily oral administration of ESL 800 mg (D14 Test) is shown below:



PK parameters of simvastatin on D1 and D14 are listed below:

Table 7: Mean plasma pharmacokinetic parameters of simvastatin at D1 *(Reference)* following a single oral administration of SIM 80 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (h)	$t_{1/2}$ (h)
N	24	24	24	24	24	24
Gmean	17,7	1,50	93,9	108	0,103	6,75
Amean	21,1	2,50	105	127	0,114	7,36
SD	14,0	3,29	47,7	68,6	0,0653	2,93
CV (%)	66,1	132	45,3	54,1	57,1	39,8
Median	16,6	1,00	112	118	0,0953	7,28
Minimum	5,34	0,50	36,5	37,0	0,0479	1,91
Maximum	60,3	12,0	213	273	0,362	14,5

N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 8: Mean plasma pharmacokinetic parameters of simvastatin at D14 *(Test)* following a single oral administration of SIM 80 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (h)	$t_{1/2}$ (h)
N	24	24	24	24	24	24
Gmean	6,89	1,62	43,3	54,6	0,0867	7,99
Amean	8,19	2,77	48,5	66,2	0,103	10,1
SD	5,21	3,40	22,5	46,6	0,0633	9,76
CV (%)	63,6	123	46,3	70,3	61,3	96,7
Median	6,68	1,25	46,4	55,3	0,0874	7,93
Minimum	2,61	0,50	15,4	16,2	0,0134	2,61
Maximum	21,7	12,0	90,4	232	0,265	51,7

N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Cmax and AUCt of simvastatin decreased by 61.1% and 49.4% following concomitant administration with ESL, respectively. Median values of Tmax of simvastatin were similar between simvastatin alone and combination with ESL.

PK parameters of simvastatin β-hydroxyacid on D1 and D14 are listed

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below:

Table 9: Mean plasma pharmacokinetic parameters of simvastatin β-hydroxyacid at D1 *(Reference)* following a single oral administration of SIM 80 mg

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (h)	$t_{1/2}$ (h)
N	24	24	24	23	23	23
Gmean	6,01	4,79	62,3	75,8	0,0928	7,47
Amean	7,93	5,73	78,5	103	0,114	9,67
SD	7,37	3,89	63,3	101	0,0651	7,94
CV (%)	93,0	67,9	80,6	98,6	57,3	82,1
Median	5,60	4,00	54,0	59,8	0,105	6,59
Minimum	1,91	1,50	20,9	21,5	0,0214	2,84
Maximum	35,3	16,0	264	468	0,245	32,35

N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 10: Mean plasma pharmacokinetic parameters of simvastatin β-hydroxyacid at D14 (*Test*) following a single oral administration of SIM 80 mg

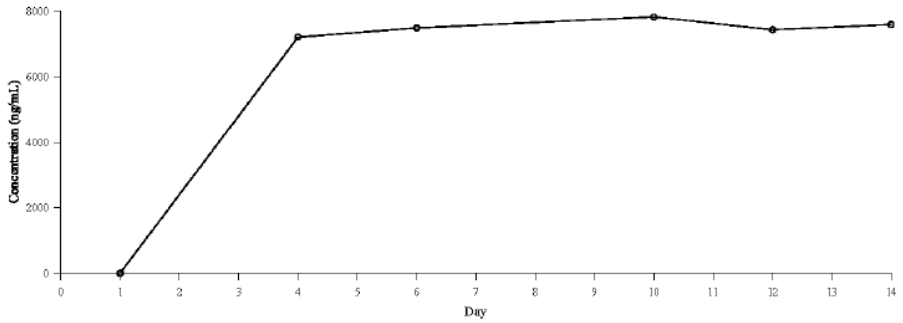
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (h)	$t_{1/2}$ (h)
N	24	24	24	24	24	24
Gmean	3,55	4,42	30,5	36,0	0,124	5,58
Amean	5,24	4,71	41,1	51,2	0,145	6,86
SD	6,16	1,94	40,5	52,2	0,0828	6,14
CV (%)	117	41,3	98,4	102	57,0	89,6
Median	2,66	4,00	28,1	32,9	0,128	5,44
Minimum	1,13	2,00	5,81	6,90	0,0208	2,03
Maximum	29,6	12,0	197	211	0,342	33,4

N = Number of subjects; Gmean = Geometric mean; Amean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Cmax and AUCt of simvastatin β-hydroxyacid decreased by 40.9% and 52.5% following concomitant administration with ESL, respectively. Median values of Tmax of simvastatin β-hydroxyacid were similar between simvastatin alone and combination with ESL.

ESL:

Mean trough plasma concentration-time profile of eslicarbazepine on D1, D4, D6, D10, D12 and D14 following once-daily oral administration of ESL 800 mg is shown below:



Mean trough plasma eslicarbazepine concentrations on Days 1, 4, 6, 10, 12, and 14 following once-daily oral administration of ESL 800 mg are

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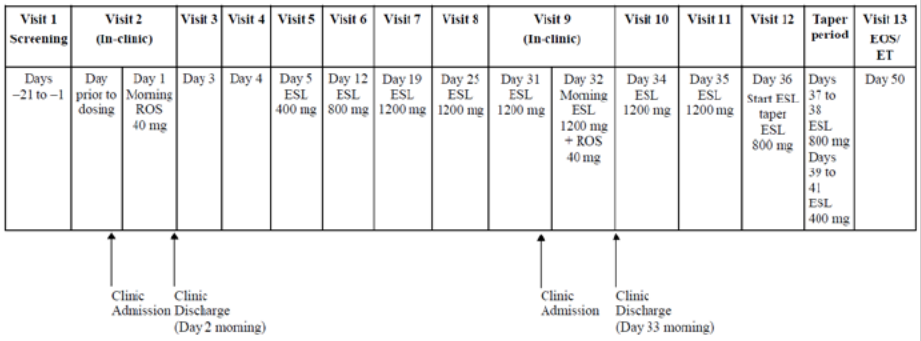
	shown below: Study Day 1 4 6 10 12 14 n 30 30 30 30 25 24 Mean (ng/mL) BLQ 7208 7491 7823 7436 7594 SD (ng/mL) - 1150 1330 1636 1595 1596 CV(%) - 16,0 17,8 20,9 21,5 21,0 n = Number of subjects; Mean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation; BLQ = Below limit of quantification Steady-state trough (i.e., pre-dose) plasma concentrations of eslicarbazepine were reached approximately 4 days of dosing and remained stable during the remaining eslicarbazepine acetate dosing period.
Safety	There was no SAE or death in the study.
Conclusion	ESL decreased systemic exposures (Cmax and AUC) of simvastatin and simvastatin β-hydroxyacid following concomitant oral once-daily administration of 800 mg ESL and single 80 mg dose of simvastatin. *ESL induces CYP3A4 with potentially-important clinical effects on plasma concentrations of drugs that are metabolized by this enzyme.*

Study **BIA-2093-150**	Effect of repeated administration of eslicarbazepine acetate on the pharmacokinetics of rosuvastatin in healthy male and female subjects.
Principal Investigator	Ralph A. Schutz, MD.
Study Center	Quintiles, Phase One Services. 6700 West 115th Street, Overland Park, KS 66211.
Study Period	2/8/11 – 6/24/11 (first subject first visit- last subject last visit)
Primary Study Objective	To investigate whether multiple-dose oral administration of eslicarbazepine acetate (ESL, 1200 mg QD) affects the pharmacokinetics of a single dose of rosuvastatin (40 mg), a substrate of CYP2C9 and possibly OATP1. *Rosuvastatin is a substrate of OATP1B1 or OATP1B3, which are uptake transporters in hepatocytes. Rosuvastatin is not extensively metabolized; ~ 10% of a radiolabeled dose is recovered as metabolite.*
Study Design and Dose Administration	This's a single-center, fixed-sequence, open-label study of the effect of repeated administration of ESL on the PK of rosuvastatin. Approximately 33 healthy male and female volunteers were to be enrolled in an effort to achieve 28 completed subjects. Subjects received the following 2 treatments: • Treatment A: A single, oral dose of 40 mg rosuvastatin. • Treatment B: ESL titration (400 mg QD orally for 7 days, then 800 mg QD for 7 days). ESL treatment, 1200 mg QD, for 14 days and a single, oral dose of 40 mg rosuvastatin on the 14th day of ESL administration followed by 3 additional days of 1200 mg QD ESL.

Reference ID: 3374277

	At the end of treatment B, subjects were tapered off ESL over a 6-day period. Subjects received ESL 800 mg QD for 3 days followed by ESL 400 mg QD for 3 days after which subjects discontinued ESL treatment. Best Available Copy The Study Schematic is shown below:  Abbreviations: EOS = end of study; ESL = eslicarbazepine acetate; ET = early termination; ROS = rosuvastatin. While subjects were in the Phase 1 unit, meals were provided at approximately 09:00 (breakfast), 12:00 (lunch), 17:00 (dinner), and 23:00 (snack). Breakfast was withheld on Days 1 and 32 to eliminate an effect of food on absorption of the study medication. Water was given as needed.
Study Population	N= 33 healthy subjects (PK population). 30 subjects completed study. 2 subjects discontinued from the study due to AEs and one was lost to follow-up. Age: 30.5 (18 – 50) years Gender: 22M/11F Race: 21 white, 11 black or African American, 1 had both white and American Indian or Alaska native.
Investigational Product	Rosuvastatin (calcium bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid]) was provided as commercially-available 40 mg tablets. Tablets were supplied as pink, oval, biconvex, coated tablets with debossed Crestor® on one side and "40" on the other side. Rosuvastatin from lot number 113522 was supplied to the site in bottles containing 30 tablets. Eslicarbazepine acetate {(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide} was provided as 400 mg tablets. Tablets were supplied as flat, white, round, noncoated tablets with no markings. Eslicarbazepine acetate from lot number CVXM was supplied to the site in bottles containing 90 tablets.
Sampling: Blood	Blood samples were collected for measurement of plasma concentrations of ESL, eslicarbazepine, (R)-licarbazepine, and rosuvastatin. PK parameters were derived only for eslicarbazepine and rosuvastatin. Blood samples were collected at predose, 30 minutes, and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours postdose on Days 1 and 32; Prior to in-clinic study drug administration on Days 12, 19, and 25.
Urine	none

Reference ID: 3374277

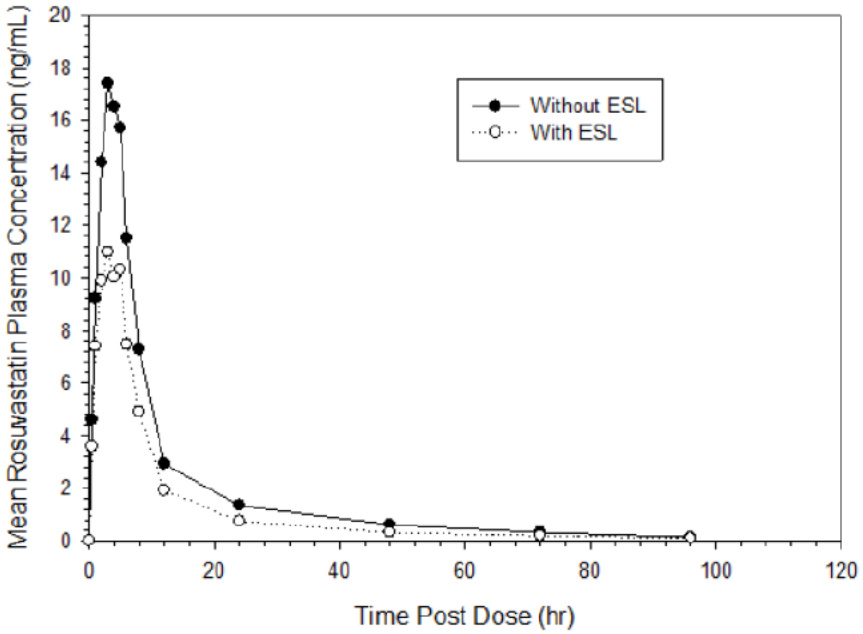
<table>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma analyses of rosuvastatin were performed by (b) (4)
Plasma analyses of eslicarbazepine were performed by (b) (4)

<table><tr><td></td><td>Rosuvastatin</td><td>BIA 2-194 (eslicarbazepine)</td></tr><tr><td>Matrix</td><td>Plasma</td><td>Plasma</td></tr><tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr><tr><td>Linear Range (ng/ml)</td><td>0.1-100</td><td>50-25000</td></tr><tr><td>LLOQ (ng/ml)</td><td>0.1</td><td>50</td></tr><tr><td>QCs (ng/ml)</td><td>0.1, 0.3, 0.8, 3.2, 13, 75.</td><td>50,150,4500,20000.</td></tr><tr><td>Inter-run precision</td><td>2.3 -11.7%</td><td>3 – 7.7%</td></tr><tr><td>Inter-run accuracy</td><td>-2.4 – 1.7 %</td><td>98.7 – 105.5%</td></tr></table>
Quality control assay validation is acceptable.</td></tr>
<tr><td>PK Assessment</td><td>Rosuvastatin: C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, λz, $t_{1/2}$, CL/F, and Vz/F (Days 1 and 32).

Eslicarbazepine: C_{max}, t_{max}, and $AUC_{0\text{-}24}$ (Day 32).

Trough plasma concentrations for eslicarbazepine acetate, eslicarbazepine, and (R)-licarbazepine.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td><u>Rosuvastatin PK</u>:
Mean plasma concentration-time profile of rosuvastatin when administered alone (Day 1) and concomitantly with ESL (Day 32) is presented below:</td></tr>
</table>

Reference ID: 3374277



All predose rosuvastatin plasma concentrations were below the limit of quantification.

PK parameters of rosuvastatin for subjects administered rosuvastatin alone on D1 and concomitantly with ESL on D32 are listed below:

Parameter	Day 1 (N=33)	Day 32 (N=33)
C_{max}[a] (ng/mL)	n = 33 19.4 (9.60)	n = 31 12.7 (7.20)
t_{max}[b] (hr)	n = 33 4.00 (2.0, 6.0)	n = 31 4.00 (1.0, 6.0)
$AUC_{0\text{-last}}$[c] (ng·hr/mL)	n = 33 183 (76.2)	n = 31 115 (47.6)
$AUC_{0\text{-}\infty}$[d] (ng·hr/mL)	n = 33 192 (78.4)	n = 30 124 (52.5)
$t_{1/2}$[e] (hr)	n = 33 22.4 (9.46)	n = 30 26.5 (16.3)
CL/F[f] (L/hr)	n = 33 241 (94.7)	n = 30 378 (145.0)
Vz/F[g] (L)	n = 33 7282 (3408.4)	n = 30 13678 (9308.1)

Abbreviations: ESL = eslicarbazepine acetate; hr = hour; SD = standard deviation.
[a] C_{max} = maximum observed concentration
[b] t_{max} = time to peak concentration. t_{max} is reported as median (minimum, maximum).
[c] $AUC_{0\text{-last}}$ = AUC from the time of drug administration (time 0) to the time of the last nonzero concentration.
[d] $AUC_{0\text{-}\infty}$ = AUC from the time of drug administration (time 0) extrapolated to infinity.
[e] $t_{1/2}$ = apparent biological half-life (estimated whenever possible), where $t_{1/2} = \ln(2)/\lambda_Z$.
[f] CL/F = apparent total clearance calculated as dose/$AUC_{0\text{-}\infty}$.
[g] Vz/F = apparent volume of distribution calculated as dose/$AUC_{0\text{-}\infty}/\lambda_Z$.
Note: Parameters are reported as mean (SD), except for t_{max}, which is reported as median (minimum, maximum).

Both Cmax and AUC of rosuvastatin were decreased by 35% by ESL. Statistical analysis of effect of ESL on rosuvastatin exposure is summarized below:

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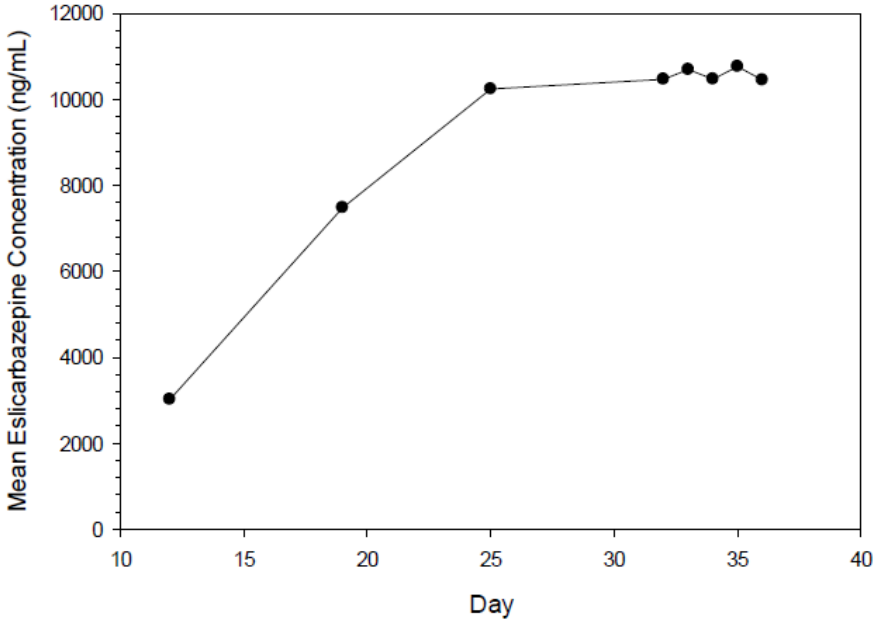
Parameter	Geometric Least Square Mean Ratio (ESL + Rosuvastatin/Rosuvastatin) (N = 33)		
	Point Estimate	90% Confidence Interval[a]	
C_{max}[b]	0.640	0.559	0.733
$AUC_{0-\infty}$[c]	0.630	0.571	0.694
AUC_{0-last}[d]	0.609	0.552	0.671

Abbreviations: ESL = eslicarbazepine acetate.
[a] The 90% confidence intervals were derived using a t-distribution.
[b] C_{max} = maximum observed concentration.
[c] $AUC_{0-\infty}$ = AUC from the time of drug administration (time 0) extrapolated to infinity.
[d] AUC_{0-last} = AUC from the time of drug administration (time 0) to the time of the last nonzero concentration.
Note: Only subjects with nonmissing assessment at both periods were analyzed (n = 31).

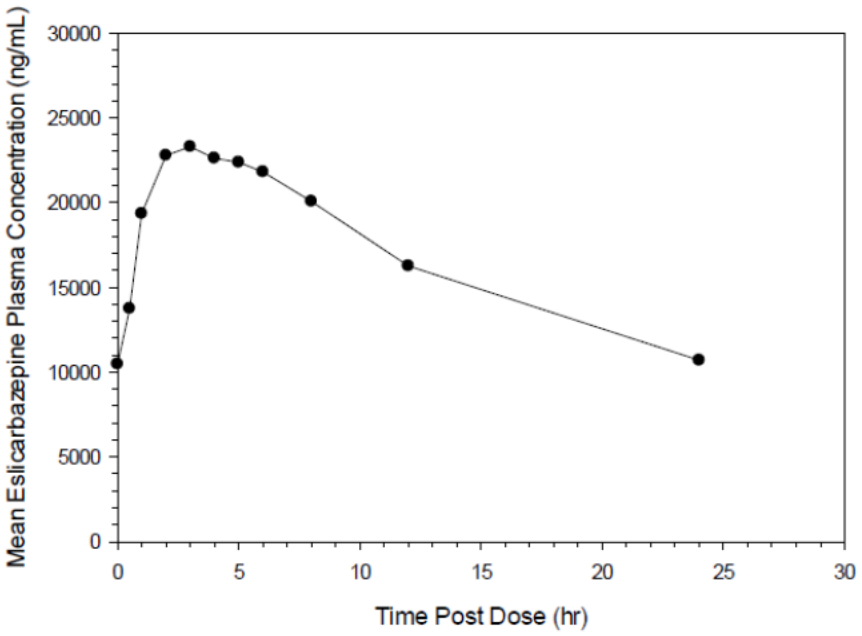
The least square mean C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ values for rosuvastatin were between 36% and 39% lower with concomitant ESL administration (Day 32) than for rosuvastatin alone (Day 1).

ESL PK:

Mean trough concentration-time profile for eslicarbazepine on Day 12 through Day 36 is shown below, which shows that steady-state was attained by Day 32 (after daily administration of ESL for 28 days).



Mean eslicarbazepine plasma concentration-time profile after multiple oral doses of ESL on Day 32 is shown below:



Mean plasma eslicarbazepine PK parameters for subjects administered rosuvastatin concomitantly with ESL on Day 32 are listed below:

Parameter	Day 32 (N=33)
C_{max}[a] (ng/mL)	n = 31 25002 (3261.5)
t_{max}[b] (hr)	n = 31 3.00 (1.0, 6.0)
AUC_{0-24}[c] (ng·hr/mL)	n = 31 401126 (52635.6)

Abbreviations: ESL = eslicarbazepine acetate; hr = hour; SD = standard deviation.
[a] C_{max} = maximum observed concentration
[b] t_{max} = time to peak concentration
[c] AUC_{0-24} = AUC from time of drug administration until 24 hours later (before next dose).
Note: Parameters are reported as mean (SD), except for t_{max}, which is reported as median (minimum, maximum).

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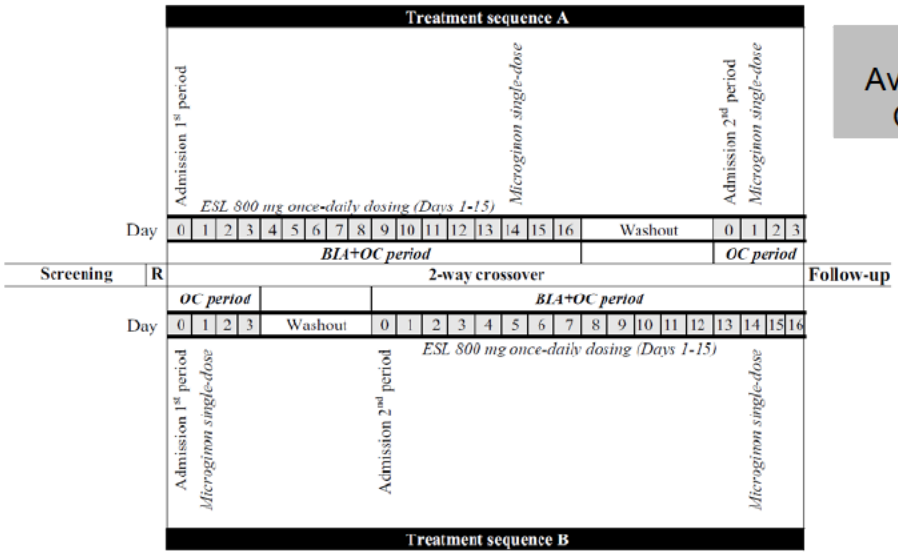
Safety	There was no SAE or death in the study. During treatment period B, 2 subjects (6.1%) discontinued from the study due to a TEAE; no subjects discontinued during treatment period A.
Conclusion	Rosuvastatin exposure (Cmax and AUC least square means) with concomitant steady-state ESL administration was 36% to 39% lower than when rosuvastatin was administered alone. *Metabolism is not a primary route of elimination for rosuvastatin. The effect of the DDI might be due to an interaction involving the uptake transporters that are responsible for rosuvastatin disposition (e.g., induction of OATP1B1 or OATP1B3).*

Study **BIA-2093-128**	Effect of repeated administration of eslicarbazepine acetate (BIA 2-093) 800 mg once daily on the pharmacokinetics of a combined oral contraceptive in healthy female subjects.
Principal	Manuel Vaz-da-Silva, MD, PhD

Investigator	
Study Center	Human Pharmacology Unit (UFH), Section of Clinical Research (SIC), Department of Research & Development (DID), BIAL – Portela & Ca, SA, 4745-457 S., Mamede do Coronado, Portugal
Study Period	9/8/08 – 11/14/08
Primary Study Objective	To investigate whether multiple-dose administration of eslicarbazepine acetate (ESL, BIA 2-093) 800 mg once-daily (QD) affects the pharmacokinetics of the components of a combined oral contraceptive (ethinyloestradiol and levonorgestrel). *The sponsor also conducted a DDI study (Study 114) with the contraceptives at 1200 mg QD of ESL (please refer to Dr.Tandon's review in DARRTS).*
Study Design and Dose Administration	Single center, two-way crossover, randomized, open-label study in 20 healthy female volunteers. The study was to be constituted by a single-dose of oral contraceptive (OC period, Microginon®) and a 15 day treatment with eslicarbazepine acetate (ESL, 800 mg QD) in which a single-dose of oral contraceptive was to be administered with the 14th dose of ESL (BIA+OC period). Both periods were to be separated by an interval of at least 3 weeks. The study design diagram is shown below:  R = Randomisation - On Days 1-13 of the BIA+OC period, subjects were to attend the research facilities early in the morning for ESL administration. - On the evening of Day 0 of the OC period and of Day 13 of the BIA+OC period, subjects were to be admitted at UFH and remained under clinical supervision until at least 48 h post Microginon® dose. On the days when subjects received single-doses of oral contraceptive (OC period and Day 14 of the BIA+OC period), subjects were to be requested to fast overnight for at least 8 hours before dosing and to remain fasted until 1 hour post-dose.
Study Population	N= 20 healthy females; PK population: 19 subjects (Subject 11 did not participate in OC period due to an AE (cutaneous rash)).

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Reference ID: 3374277

<table>
<tr><td></td><td>Age: 28.15 (20 – 40) years
Gender: 20F
Race: no information.</td></tr>
<tr><td>Investigational Product</td><td>- Coated tablets containing 30 µg ethinyloestradiol and 150 µg levonorgestrel (Microginon®, marketed by Bayer Portugal S.A., Portugal).
- Tablets containing ESL strength 800 mg. Tablets were manufactured in accordance with Good Manufacturing Practice (GMP) by BIAL - Portela & Ca, SA.
<table><tr><td></td><td>Batch number</td></tr><tr><td>ESL 800 mg tablets</td><td>060158-L</td></tr><tr><td>Microginon® tablets</td><td>74894</td></tr></table></td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples (5 mL) for the assay of plasma eslicarbazepine (BIA 2-194) were taken at pre-dose, on Days 1, 4, 6, 10, 14 and 15 of the BIA+OC period.
Blood samples (7 mL) for the assay of plasma ethinyloestradiol and levonorgestrel were taken on both study periods at the following times: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma analyses of levonorgestrel, ethinyloestradiol and BIA 2-194 were performed by (b) (4)
<table><tr><td></td><td>BIA 2-194 (eslicarbazepine)</td><td>Ethinyloestradiol</td><td>Levonorgestrel</td></tr><tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr><tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr><tr><td>Linear Range</td><td>50 – 25000 ng/ml</td><td>3 – 300 pg/ml</td><td>0.05 – 10 ng/ml</td></tr><tr><td>LLOQ</td><td>50 ng/ml</td><td>50 pg/ml</td><td>50 ng/ml</td></tr><tr><td>QCs</td><td>50, 140, 10000, 20000 ng/ml</td><td>3, 8.4, 120, 240 pg/ml</td><td>0.05, 0.14, 4, 8 ng/ml.</td></tr><tr><td>Inter-run precision</td><td>2.6% - 8.6%</td><td>3.1% - 7.3%</td><td>2% - 6.9%</td></tr><tr><td>Inter-run accuracy</td><td>97.6% - 106.1%</td><td>99.6% - 104.6%</td><td>94.8% - 99.7%</td></tr></table>
Quality control assay validation is acceptable.</td></tr>
<tr><td>PK Assessment</td><td>PK parameters for ethinyloestradiol and levonorgestrel: C_{max}, t_{max}, AUC_{0-t} , AUC_{0-24} , $AUC_{0-\infty}$, λz, $t_{1/2}$.
Trough plasma concentrations for eslicarbazepine.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results</td><td>Following a single dose of Microginon® administered alone (Reference) and following a single dose of Microginon® administered concomitantly with the 14th dose of a 15-day once-daily 800 mg eslicarbazepine acetate administration period (Test), the levonorgestrel and ethinyloestradiol plasma concentration versus time profiles are</td></tr>
</table>

Reference ID: 3374277

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shown below:

Figure B. Mean plasma Levonorgestrel concentration-time profile following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of ESL 800 mg once-daily (*Test*) and following administration of a single-dose of Microginon® administered alone (*Reference*) (n=19)

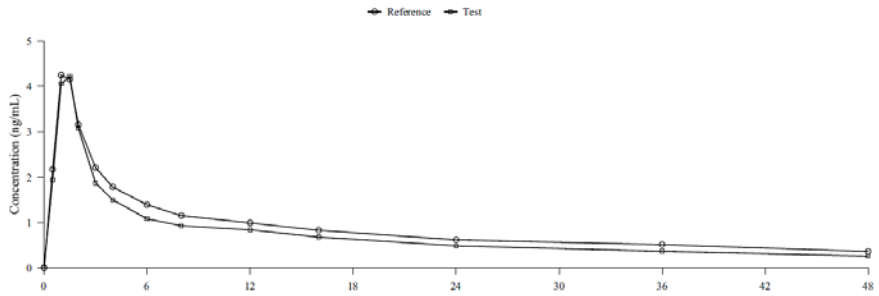
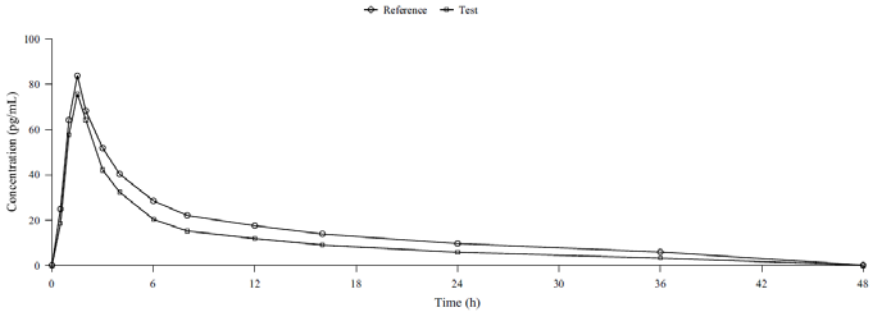


Figure C. Mean plasma Ethinyloestradiol concentration-time profile following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of ESL 800 mg once-daily (*Test*) and following administration of a single-dose of Microginon® administered alone (*Reference*) (n= 19)



Mean PK parameters of ethinyloestradiol following administration of a single-dose of Microginon® concomintantly with the 14th dose of a 15-day oral regimen of ESL 800 mg once-daily (test) and following administration of a single-dose od Microginon® administered alone (reference) (n=19) are listed below:

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Test

	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	AUC_{0-24} (pg.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
N	19	19	19	19	19	19	19
Gmean	75.0	1.50	453	533	409	0.0523	13.3
Amean	77.9	1.53	483	562	425	0.0544	13.7
SD	20.9	0.262	167	181	114	0.0167	3.55
CV%	26.8	17.2	34.5	32.2	26.9	30.7	25.9
Median	74.6	1.50	484	558	430	0.0501	13.8
Minimum	38.3	1.00	249	311	249	0.0336	7.09
Maximum	115	2.00	773	871	568	0.0978	20.6

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Reference

	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	AUC_{0-24} (pg.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
N	19	19	19	19	19	19	19
Gmean	82.4	1.50	665	768	547	0.0459	15.1
Amean	85.5	1.53	692	797	564	0.0468	15.5
SD	23.4	0.262	195	223	136	0.0095	3.51
CV%	27.4	17.2	28.3	28.0	24.1	20.2	22.7
Median	87.4	1.50	676	791	551	0.0493	14.0
Minimum	49.3	1.00	406	514	319	0.0312	11.3
Maximum	139	2.00	1097	1347	768	0.0612	22.2

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Mean PK parameters of levonorgestrel following administration of a single-dose of Microginon® concomintantly with the 14th dose of a 15-day oral regimen of ESL 800 mg once-daily (test) and following administration of a single-dose od Microginon® administered alone (reference) (n=19) are listed below:

Test

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
n	19	19	19	19	19	19	19
Gmean	4.34	1.16	32.0	43.1	23.8	0.0255	27.2
Amean	4.62	1.21	34.7	45.6	25.8	0.0273	30.0
SD	1.53	0.346	12.9	13.3	9.87	0.0091	16.5
CV%	33.1	28.6	37.2	29.2	38.2	33.4	55.2
Median	4.74	1.00	36.3	49.0	26.8	0.0264	26.2
Minimum	1.65	0.50	9.55	11.9	7.15	0.0089	15.9
Maximum	6.98	2.00	57.2	66.2	42.1	0.0436	77.6

= Unreliable value; period over which rate constant was calculated was systematically < 2 times the resulting half-life; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Reference

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
n	19	19	19	19	19	19	19
Gmean	4.17	1.26	37.4	52.1	26.8	0.0239	29.0
Amean	4.54	1.29	42.1	56.8	30.2	0.0247	30.1
SD	1.72	0.303	19.1	22.1	13.9	0.0060	9.19
CV%	37.9	23.5	45.3	38.9	45.9	24.3	30.5
Median	5.11	1.50	43.5	60.6	29.5	0.0248	27.9
Minimum	1.65	1.00	11.3	19.2	8.35	0.0126	21.1
Maximum	7.55	2.00	76.6	94.4	53.8	0.0329	55.1

= Unreliable value; period over which rate constant was calculated was systematically < 2 times the resulting half-life; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

For ethinyloestriol, mean systemic exposures were decreased by 9% for Cmax and 30% for AUCt following concomitant administration with ESL at 800 mg QD, respectively; for levonorgestrel, mean systemic exposures were decreased by 2% for Cmax and 18% for

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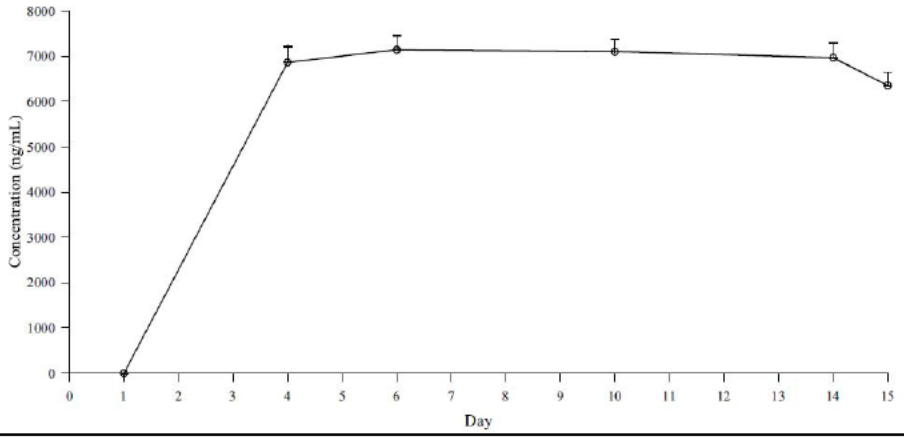
	AUCt following concomitant administration with ESL at 800 mg QD, respectively. Point estimate and 90% CI for the comparison of major PK parameters of levonorgestrel and ethnyloestadiol are summarized below: **Levonorgestrel** 			Levonorgestrel *Test/Reference*	Post-hoc Power
---	---	---	---
$AUC_{0-\infty}$ (ng.h/mL)	PE 90% CI	82.97 75.63; 91.03	98.73%
AUC_{0-24} (pg.h/mL)	PE 90% CI	89.19 82.29; 96.66	99.66%
C_{max} (ng/mL)	PE 90% CI	104.09 95.24; 113.78	99.11% | **Ethinyloestradiol** |		Ethinyloestradiol *Test/Reference*	Post-hoc Power
---	---	---	---
$AUC_{0-\infty}$ (pg.h/mL)	PE 90% CI	69.39 64.32; 74.86	99.82%
AUC_{0-24} (pg.h/mL)	PE 90% CI	74.73 70.79; 78.90	99.99%
C_{max} (pg/mL)	PE 90% CI	91.16 85.25; 97.48	99.96%	 PE = Point Estimate; CI = Confidence Interval. Steady-state trough (i.e., pre-dose) plasma concentrations of BIA 2-194 (eslicarbazepine or S-licarbazepine), the main ESL metabolite, were reached approximately within 4 days of dosing and remained stable during the remaining eslicarbazepine acetate dosing period: 
Safety	There was no SAE or death in the study.
Conclusion	Mean levonorgestrel Cmax increased 4% (Test/Reference PE = 104.09; 90%CI = 95.24-113.78) and AUC0-24 decreased 11% (PE = 89.19; 90%CI = 82.29-96.66) following administration of ESL 800 mg. In the previous study with ESL 1200 mg, mean levonorgestrel Cmax decreased 13% and AUC0-24 decreased 37%. Mean ethinyloestradiol Cmax decreased 9% (Test/Reference PE = 91.16; 90%CI = 85.25-97.48) and AUC0-24 decreased 25% (PE = 74.73; 90%CI = 70.79-78.90) following administration of ESL 800 mg. In the previous study with ESL 1200 mg, mean ethinyloestradiol Cmax decreased 20% and AUC0-24 decreased 42%. Tmax values were similar for levonorgestrel and ethinyloestradial

	following administration of ESL at 800 mg QD. The induction of the ethinyloestradiol and levonorgestrel metabolism by ESL is likely dependent on the ESL dose and concomitant administration of ESL 800 mg with hormonal contraceptives may still render these contraceptives less effective.

PK in Healthy Subjects

Study **BIA-2093-127**	A phase I, monocentre, open, randomised, parallel study to evaluate the pharmacokinetics and tolerability of multiple doses of eslicarbazepine acetate and oxcarbazepine in healthy subjects
Principal Investigator	L. Cavens, MD
Study Center	SGS Life Science Services, Clinical Pharmacology Unit, Lange Beeldekensstraat 267, B-2060 Antwerp, Belgium
Study Period	11/14/08 – 2/7/09
Primary Study Objective	To evaluate the steady-state cerebrospinal fluid (CSF) versus plasma concentrations of parent drug and metabolites following oral administration of eslicarbazepine acetate (ESL) and oxcarbazepine (OXC) to healthy subjects. Rationale of the study: Both ESL and OXC exert their anti-epileptic action in the CNS. ESL and OXC active metabolites are formed in the periphery and have to cross the blood-brain barrier to be active. It is unknown whether the metabolites differ in ability to cross the blood-brain barrier and how the cerebrospinal fluid (CSF) concentrations correlate with their plasma concentrations.
Study Design and Dose Administration	Mono-centre, open label, randomized, multiple doses, parallel study in healthy male and female subjects. Subjects were randomized to one of 2 treatment groups (Group A and Group B) and received study medication as follows: • Group A: 600 mg ESL once daily (q.d). (morning) from Day 1 to Day 3 and 1200 mg ESL q.d. (morning) from Day 4 to Day 9; • Group B: 300 mg OXC twice daily (b.i.d.) from Day 1 to Day 3 and 600 mg OXC b.i.d. from Day 4 to Day 9 (Day 9; only morning dose). 600 mg b.i.d. regimen is commonly used in the maintenance therapy of adult subjects with epilepsy for OXC. Subjects were asked to come to the clinical center every day from Day 1 to Day 8 for study medication administration. On Day 8 (evening), subjects were confined for a period of approximately 60 h (until the morning of Day 11). Study medication was taken orally in fasted condition.
Study Population	Twelve subjects (6 males and 6 females) were planned, 14 subjects were included and randomized (7 males and 7 females) and 13 subjects completed the study.

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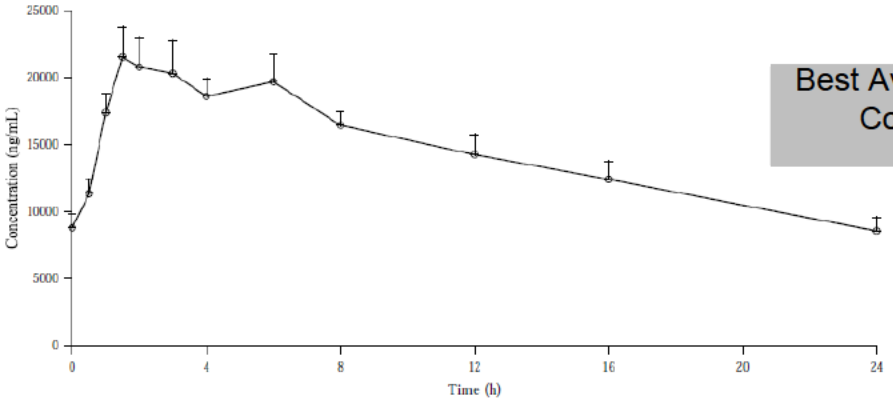
<table>
<tr><td></td><td>Age: 46 (26 – 54) years
Gender: 7M/7F
Race: 13 white, and 1 Asian.</td></tr>
<tr><td>Investigational Product</td><td>
<table>
<tr><th></th><th>Batch numbers</th><th>Expiry date</th></tr>
<tr><td>Eslicarbazepine acetate (BIAL - Portela & Ca)</td><td>060157-L</td><td>October 2009</td></tr>
<tr><td>Oxcarbazepine (Trileptal®, Novartis Pharma)</td><td>T0355</td><td>May 2011</td></tr>
</table>
</td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples for ESL (Group A) and OXC (Group B) and metabolites level determination were collected on Day 1 pre-dose and Day 9 pre-dose and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose (16 and 24 h post-dose only in the ESL group).</td></tr>
<tr><td>CSF</td><td>CSF samples for ESL (Group A) and OXC (Group B) and metabolites level determination were collected on Day 9 pre-dose and 30 min, 1, 2, 4,6, 8, 12, 16 and 24 h post-dose (16 and 24 h post-dose only in the ESL group). Ten (Group A: ESL) and 8 (Group A: OXC) CSF samples (approximately 1.5 mL) for determination of ESL, BIA 2-194, BIA 2-195 and OXC were taken by lumbar puncture over 24 h (Group A: ESL) and 12 h (Group B: OXC).</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>The assay of ESL, BIA 2-194, BIA 2-195 and OXC in plasma and CSF were performed by (b) (4)
Plasma:
<table>
<tr><th></th><th>BIA 2-093 (parent)</th><th>BIA 2-194 (eslicarbazepine)</th><th>BIA 2-195 (R-licarbazepine)</th><th>OXC</th></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>50 - 1000</td><td>50 - 25000</td><td>50 - 25000</td><td>50 - 1000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>50</td><td>50</td><td>50</td><td>50</td></tr>
<tr><td>QCs (ng/ml)</td><td>50, 150, 450, 800.</td><td>50, 150, 4500, 20000.</td><td>50, 150, 4500, 20000.</td><td>50, 150, 450, 800.</td></tr>
<tr><td>Inter-run precision</td><td>2.5% - 9.7%</td><td>3% - 7.7%</td><td>2.7% - 12.1%</td><td>3.8% - 5.7%</td></tr>
<tr><td>Inter-run accuracy</td><td>98.7% - 104.4%</td><td>98.7% - 105.5%</td><td>98.7% - 106.7%</td><td>102.6% - 104.3%</td></tr>
</table>
CSF:
<table>
<tr><th></th><th>BIA 2-093 (parent)</th><th>BIA 2-194 (eslicarbazepine)</th><th>BIA 2-195 (R-licarbazepine)</th><th>OXC</th></tr>
<tr><td>Matrix</td><td>CSF</td><td>CSF</td><td>CSF</td><td>CSF</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>10 - 1000</td><td>10 - 10000</td><td>10 - 10000</td><td>10 - 1000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
</table>
</td></tr>
</table>

Reference ID: 3374277

	<table><tr><td>QCs (ng/ml)</td><td>10, 30, 200, 800.</td><td>10, 30, 500, 8000.</td><td>10, 30, 500, 8000.</td><td>10, 30, 200, 800.</td></tr><tr><td>Inter-run precision</td><td>3.2 % - 8.8%</td><td>3.2% - 9.2%</td><td>5.2% - 12.5%</td><td>3.8% - 11.9%</td></tr><tr><td>Inter-run accuracy</td><td>97.1% - 106.6%</td><td>98.4% - 106.4%</td><td>95.6% - 100.7%</td><td>101.2% - 110.2%</td></tr></table> Quality control assay validation is acceptable.
PK Assessment	The following pharmacokinetic parameters for ESL, BIA 2-194 (S-licabazepine), BIA 2-195 (L-licabazepine) and OXC were derived by non-compartmental analysis from the plasma and CSF concentration versus time profiles: lag time (tlag), maximum observed drug concentration (Cmax), time at which Cmax occurred (tmax), minimum observed drug concentration (Cmin), area under the concentration versus time curve (AUC) from time zero to the last sampling time at which concentrations were at or above the limit of quantification (AUC0-t), AUC over the dosing interval (AUC0-τ), AUC from time zero to infinity (AUC0-∞), apparent terminal elimination rate constant (λz), apparent terminal elimination half-life (t1/2), and fluctuation.
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none
Pharmacokinetic Results	<u>Plasma PK of ESL and its metabolites</u> ESL plasma and CSF levels were BLOQ in almost all the situations and sampling times. *BIA 2-194 (S-licabazepine) PK*: Mean (±SEM) plasma BIA 2-194 concentration-time profile on Day 9 following oral administration of ESL 1200 mg q.d. is presented below:  Mean plasma PK parameters of BIA 2-194 on Day 9 following oral administration of ESL 1200 mg QD are shown below:

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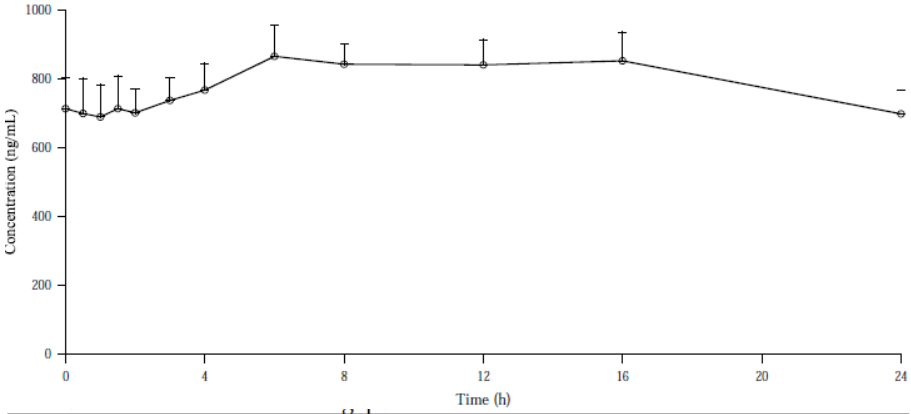
Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	7	7	7
G_{mean}	-	23932	2.07	8125	340123	340123	532852	15.8	109
A_{mean}	0.00	24698	2.43	8417	345962	345962	546919	15.9	113
SD	-	6630	1.69	2696	70412	70412	143594	2.23	33.7
CV (%)	-	26.8	69.7	32.0	20.4	20.4	26.3	14.0	29.8
Median	-	23037	2.00	7858	332345	332345	500831	14.9	101
Minimum	-	16710	1.00	5952	256729	256729	381512	13.8	80.4
Maximum	-	33172	6.00	14245	467172	467172	841544	19.2	174

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

BIA 2-195 (L-licabazepine) PK:

Mean (±SEM) plasma BIA 2-195 concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of ESL 1200 mg q.d. are presented below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	6	6	7
G_{mean}	-	886	6.04	625	18743	18743	72803	54.9	32.2
A_{mean}	0.00	911	8.36	642	19182	19182	89530	64.1	33.2
SD	-	235	4.82	171	4620	4620	75251	41.7	9.16
CV (%)	-	25.8	57.7	26.7	24.1	24.1	84.1	65.1	27.6
Median	-	850	8.00	598	17389	17389	57376	45.5	29.0
Minimum	-	661	0.50	504	14746	14746	40717	28.4	24.4
Maximum	-	1285	16.0	1001	26918	26918	238892	137	45.5

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

OXC PK:

Mean (±SEM) plasma OXC concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of ESL 1200 mg q.d. are presented below, respectively:

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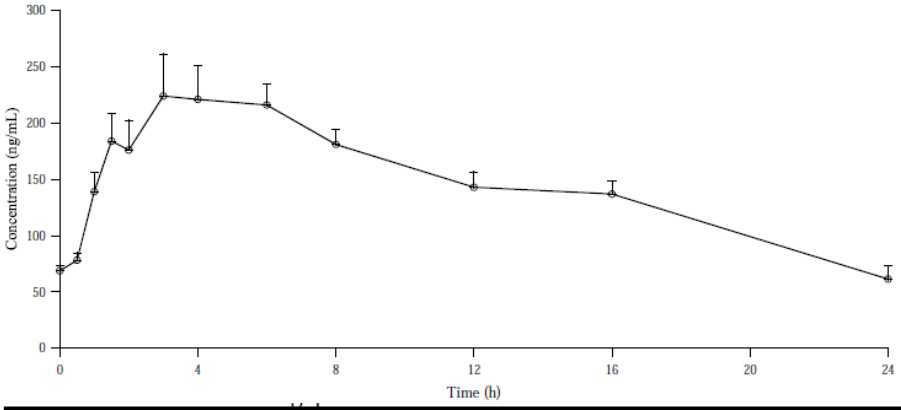


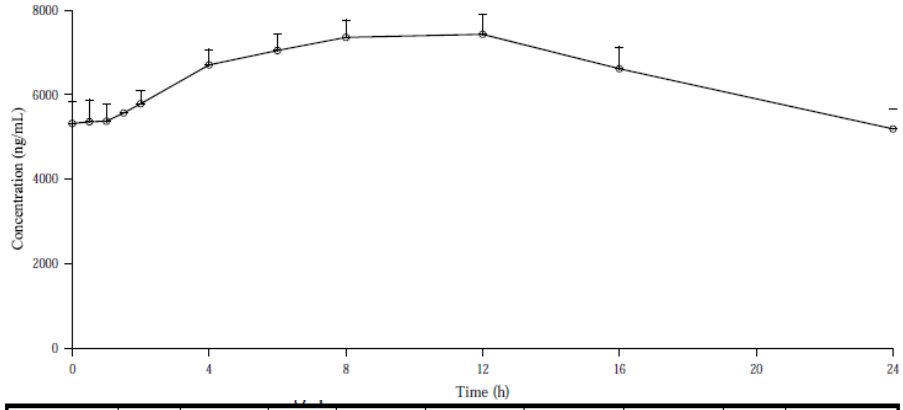
Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	7	7	7
G_{mean}	-	245	3.26	-	3377	3469	4610	10.6	129
A_{mean}	0.00	253	3.71	56.5	3445	3520	4675	10.7	133
SD	-	72.6	1.80	26.8	762	679	846	2.28	35.2
CV (%)	-	28.7	48.4	47.5	22.1	19.3	18.1	21.2	26.4
Median	-	222	3.00	66.7	3419	3419	4779	9.94	137
Minimum	-	194	1.00	0.00	2541	2882	3604	9.18	89.2
Maximum	-	396	6.00	81.9	4826	4826	6001	15.8	193

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

CSF PK of ESL and its metabolites

BIA 2-194 (S-licabazepine) PK:

Mean (±SEM) CSF BIA 2-194 concentration-time profile and mean CSF PK parameters on Day 9 following oral administration of ESL 1200 mg q.d. are shown below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	5	5	6
G_{mean}	-	7559	10.0	4944	154509	154509	335871	23.8	39.1
A_{mean}	0.00	7616	10.7	5027	155777	155777	353598	24.8	40.6
SD	-	1050	3.93	1054	22495	22495	134643	8.08	12.1
CV (%)	-	13.8	36.9	21.0	14.4	14.4	38.1	32.6	29.8
Median	-	7052	12.0	4949	150183	150183	308657	20.36	40.9
Minimum	-	6849	6.00	4058	135517	135517	245969	17.28	27.6
Maximum	-	9238	16.0	6997	195126	195126	573077	35.60	53.3

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

% CSF AUC extrapolation is 56% for estimation of CSF AUCinf. The

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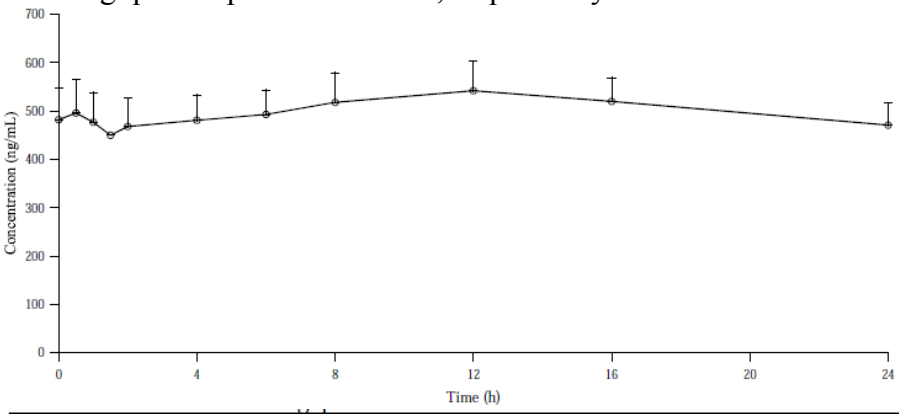
values of AUCinf and T1/2 are not reliable, which is due to the short-period sample collection.

BIA 2-195 (L-licabazepine) PK:

Mean (±SEM) CSF BIA 2-195 concentration-time profile and mean CSF PK parameters on Day 9 following oral administration of ESL 1200 mg q.d. are presented below, respectively:

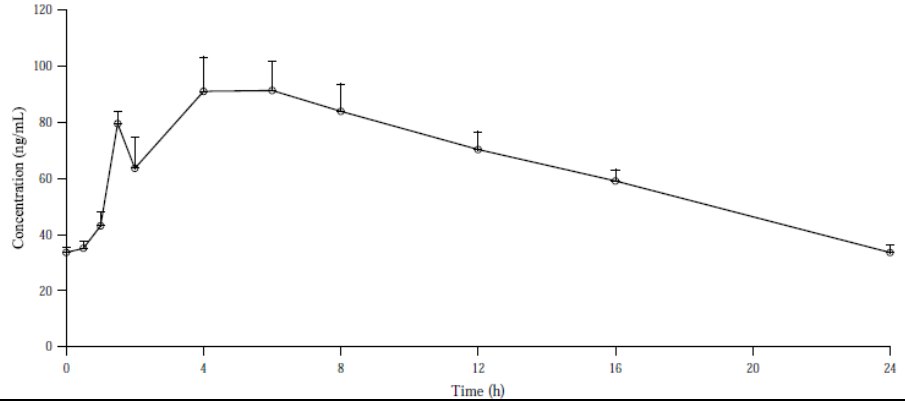


Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	4	4	6
G_{mean}	-	538	7.78	440	11791	11791	51325	56.8	19.4
A_{mean}	0.00	553	11.4	451	12072	12072	59335	61.8	20.1
SD	-	145	5.70	115	2909	2909	41138	32.1	5.61
CV (%)	-	26.2	49.9	25.6	24.1	24.1	69.3	52.0	28.0
Median	-	515	12.0	416	11280	11280	41715	48.7	19.6
Minimum	-	385	0.50	327	8475	8475	33312	40.5	12.0
Maximum	-	789	16.0	658	16691	16691	120599	109	26.7

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

OXC PK:

Mean (±SEM) CSF OXC concentration-time profile and mean CSF PK parameters on Day 9 following oral administration of ESL 1200 mg q.d. are presented below, respectively:



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Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	6	6	6
Gmean	-	93.2	5.14	30.7	1522	1522	2047	10.9	97.1
Amean	0.00	96.1	5.67	30.9	1543	1543	2073	10.9	99.0
SD	-	27.0	3.20	3.65	287	287	368	0.690	21.3
CV (%)	-	28.0	56.5	11.8	18.6	18.6	17.8	6.34	21.5
Median	-	90.3	4.00	29.7	1520	1520	2019	11.0	95.5
Minimum	-	67.8	4.00	26.4	1221	1221	1659	9.62	76.8
Maximum	-	141	12.0	35.5	2038	2038	2690	11.7	124

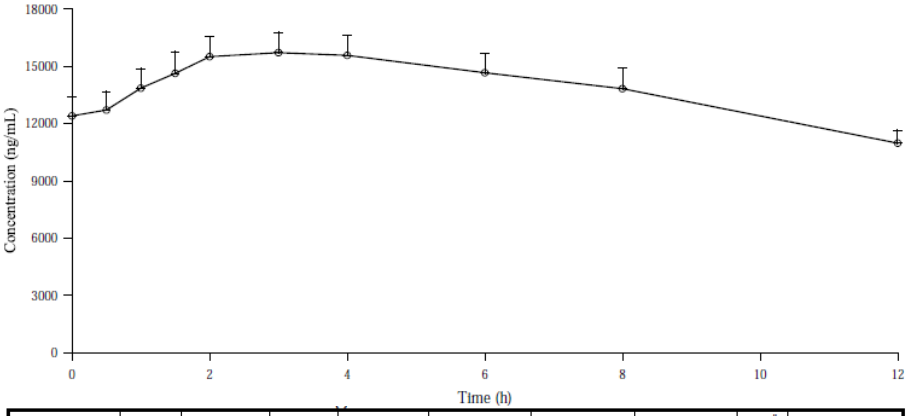
= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

<u>Plasma PK of OXC and its metabolites</u>

Neither mean nor individual plasma concentration-time profiles for ESL are displayed because plasma levels were below the limit of quantification in all situations and at all sampling times.

BIA 2-194 (S-licabazepine) PK:

Mean (±SEM) plasma BIA 2-194 concentration-time profile and plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	7	7	7
G_{mean}	-	16162	2.90	10801	164726	164726	401648	15.0	38.5
A_{mean}	0.00	16353	3.00	10945	167160	167160	406100	15.2	39.0
SD	-	2662	0.816	1843	29904	29904	64163	2.20	6.40
CV (%)	-	16.3	27.2	16.8	17.9	17.9	15.8	14.5	16.4
Median	-	16796	3.00	11524	177421	177421	413380	15.5	40.9
Minimum	-	12481	2.00	8191	121162	121162	313852	11.4	30.4
Maximum	-	20053	4.00	13093	204194	204194	497169	18.2	46.2

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

BIA 2-195 (L-licabazepine) PK:

Mean (±SEM) plasma BIA 2-195 concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:

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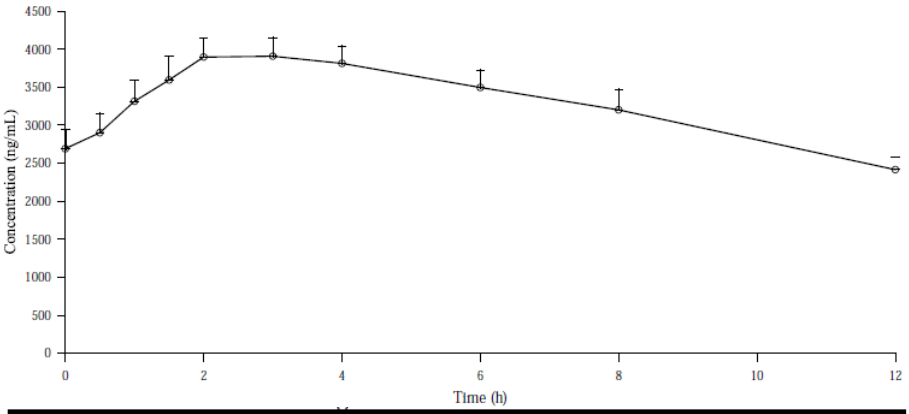
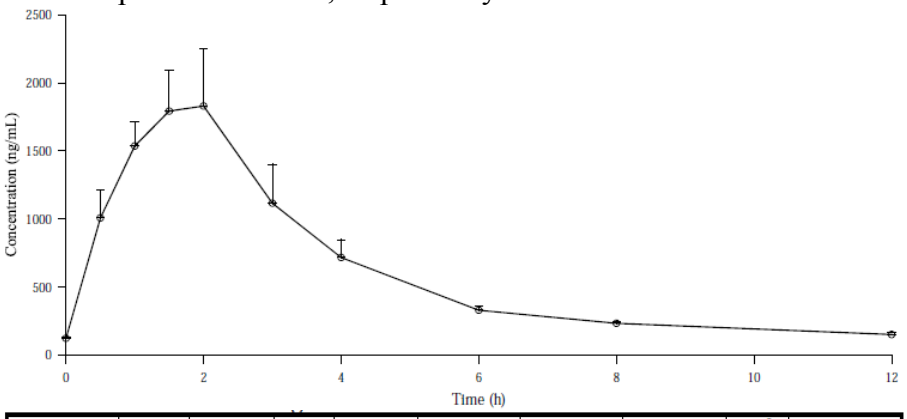


Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	7	7	7
G_{mean}	-	4039	2.90	2377	39034	39034	79360	11.6	50.2
A_{mean}	0.00	4077	3.00	2409	39564	39564	80279	11.7	51.1
SD	-	613	0.816	426	7094	7094	13149	1.30	10.3
CV (%)	-	15.0	27.2	17.7	17.9	17.9	16.4	11.1	20.2
Median	-	3721	3.00	2427	36984	36984	81534	12.1	50.7
Minimum	-	3425	2.00	1879	31759	31759	64224	9.8	36.9
Maximum	-	4929	4.00	2998	49318	49318	98830	12.9	65.0

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

OXC PK:

Mean (±SEM) plasma OXC concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	7	7	7	7	7	7	7	7	7
G_{mean}	-	1990	1.37	123	7135	7135	8517	5.57	312
A_{mean}	0.00	2129	1.43	124	7439	7439	8749	5.81	315
SD	-	941	0.450	18.0	2561	2561	2369	1.79	43.8
CV (%)	-	44.2	31.5	14.5	34.4	34.4	27.1	30.8	13.9
Median	-	1804	1.50	126	6672	6672	8544	5.75	303
Minimum	-	1287	1.00	102	5175	5175	6585	3.48	255
Maximum	-	1804	1.50	126	6672	6672	8544	5.75	303

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

<u>CSF PK of OXC and its metabolites</u>

Neither mean nor individual CSF concentration-time profiles for ESL are

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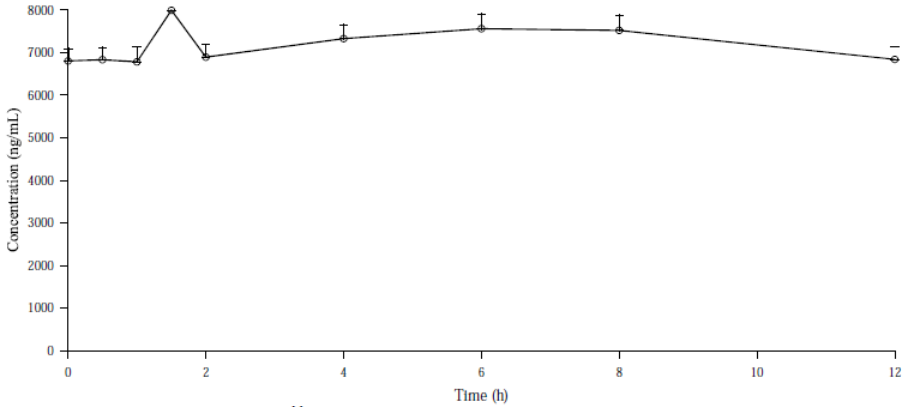
displayed because CSF levels were below the limit of quantification in almost all situations and sampling times.

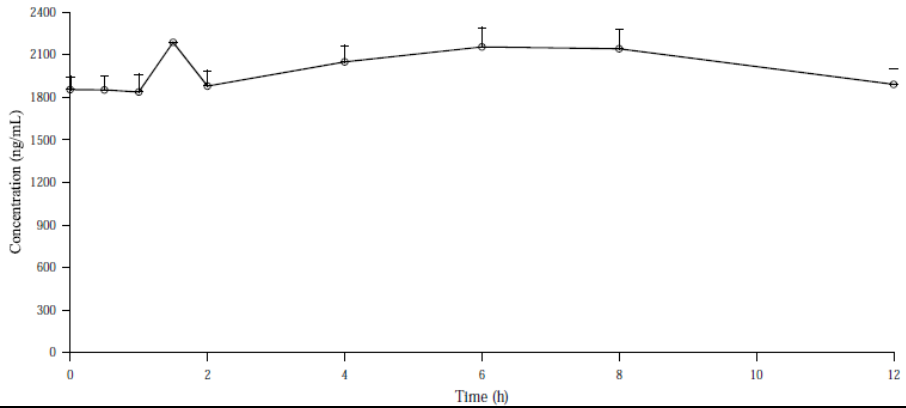
BIA 2-194 (S-licabazepine) PK:
Mean (±SEM) CSF BIA 2-194 concentration-time profile and plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	5	5	6
G_{mean}	-	7566	5.00	6530	86187	86187	567488	47.4	14.3
A_{mean}	0.00	7610	5.58	6567	86608	86608	633854	56.4	14.4
SD	-	912	2.15	779	9545	9545	350905	41.2	2.13
CV (%)	-	12.0	38.6	11.9	11.0	11.0	55.4	73.0	14.8
Median	-	7478	6.00	6498	85567	85567	614170	43.6	14.3
Minimum	-	6410	1.50	5678	74540	74540	308981	22.8	11.8
Maximum	-	9146	8.00	7964	103392	103392	1214758	127	17.3

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

BIA 2-195 (L-licabazepine) PK:
Mean (±SEM) CSF BIA 2-195 concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:



Reference ID: 3374277

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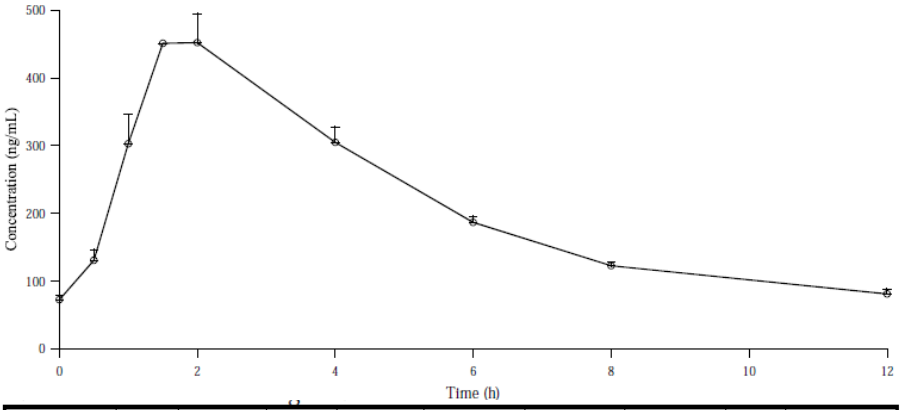
Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}^{\#}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	5	5	6
G_{mean}	-	2146	6.60	1769	23996	23996	115151	33.2	18.5
A_{mean}	0.00	2166	6.67	1785	24201	24201	127217	40.1	18.8
SD	-	327	1.03	260	3495	3495	72905	32.0	3.98
CV (%)	-	15.1	15.5	14.6	14.4	14.4	57.3	79.9	21.1
Median	-	2098	6.00	1671	23369	23369	95916	25.5	18.7
Minimum	-	1782	6.00	1564	20570	20570	80995	21.5	12.7
Maximum	-	2562	8.00	2114	28778	28778	236042	88.0	25.3

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

OXC PK:

Mean (±SEM) CSF OXC concentration-time profile and mean plasma PK parameters on Day 9 following oral administration of OXC 600 mg b.i.d. are presented below, respectively:



Parameter	t_{la} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	Fluctuation (%)
N	6	6	6	6	6	6	6	6	6
G_{mean}	-	448	1.91	70.9	2485	2485	2989	4.21	181
A_{mean}	0.00	459	1.92	72.3	2513	2513	3016	4.25	182
SD	-	109	0.204	17.1	400	400	440	0.605	24.8
CV (%)	-	23.7	10.6	23.6	15.9	15.9	14.6	14.3	13.6
Median	-	466	2.00	65.7	2590	2590	3006	4.39	184
Minimum	-	305	1.50	63.4	1936	1936	2475	3.23	149
Maximum	-	589	2.00	107	2890	2890	3613	4.88	220

N = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

<u>Comparison of plasma versus CSF PK profile within ESL treatment group (Group A):</u>

BIA 2-194 (S-licabazepine):

Mean plasma versus CSF BIA 2-194 concentration-time profile on Day 9 following oral administration of ESL 1200 mg q.d. is shown below:

Reference ID: 3374277

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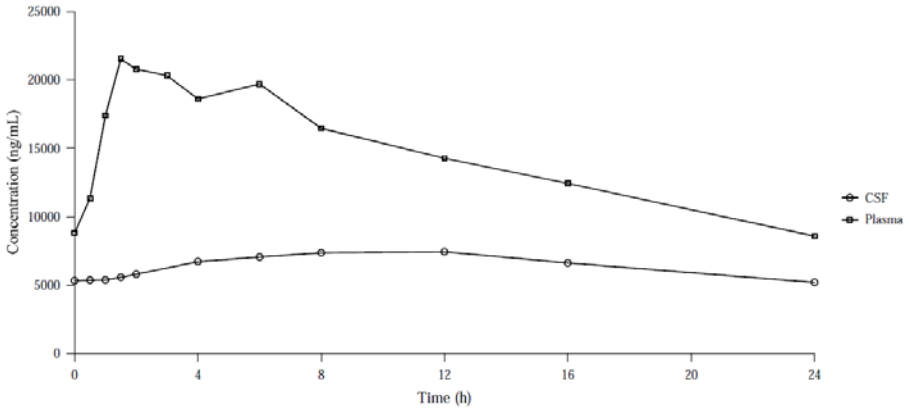
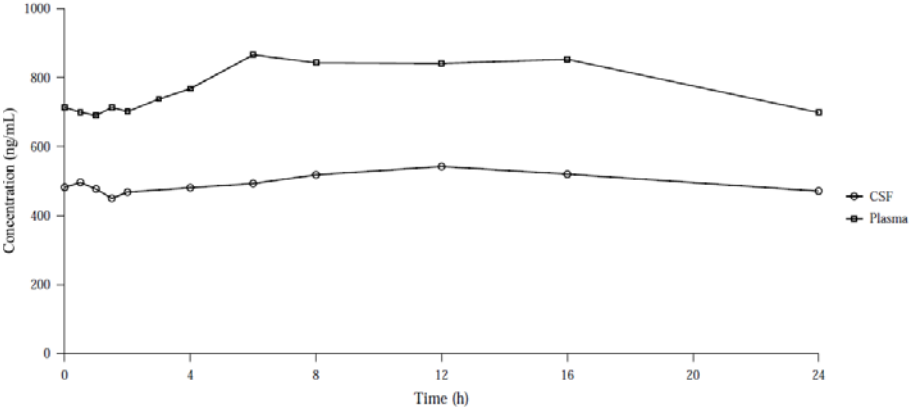


Point estimates and 90% confidence intervals for the comparison of CSF versus plasma pharmacokinetic parameters of BIA 2-194 following oral administration of ESL 1200 mg q.d. are summarized below:

BIA 2-194 - CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	31.58 25.35; 39.35
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	45.43 38.21; 54.00

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0153) were found.

BIA 2-195 (L-licabazepine):
Mean plasma versus CSF BIA 2-195 concentration-time profile on Day 9 following oral administration of ESL 1200 mg q.d. is shown below:



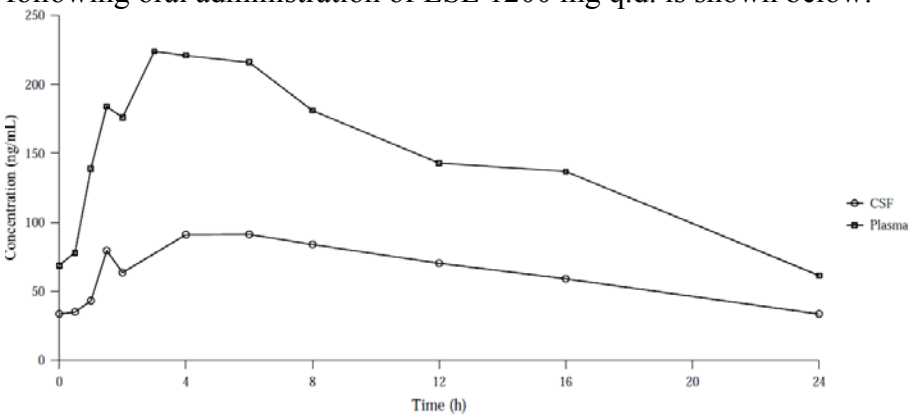
Point estimates and 90% confidence intervals for the comparison of CSF versus plasma pharmacokinetic parameters of BIA 2-195 following oral administration of ESL 1200 mg q.d. are summarized below:

Reference ID: 3374277

BIA 2-195 CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	60.76 47.23; 78.18
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	62.91 49.87; 79.35

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

OXC:
Mean plasma versus CSF OXC concentration-time profile on Day 9 following oral administration of ESL 1200 mg q.d. is shown below:



Point estimates and 90% confidence intervals for the comparison CSF versus plasma pharmacokinetic parameters of OXC following oral administration of ESL 1200 mg q.d. are summarized below:

OXC - CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	38.00 29.21; 49.44
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	43.86 36.65; 52.50

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

<u>Comparison of plasma versus CSF PK profile within OXC treatment group (Group B):</u>

BIA 2-194 (S-licabazepine):
Mean plasma versus CSF BIA 2-194 concentration-time profile on Day 9 following oral administration of OXC 600 mg b.i.d. is hown below:

Reference ID: 3374277

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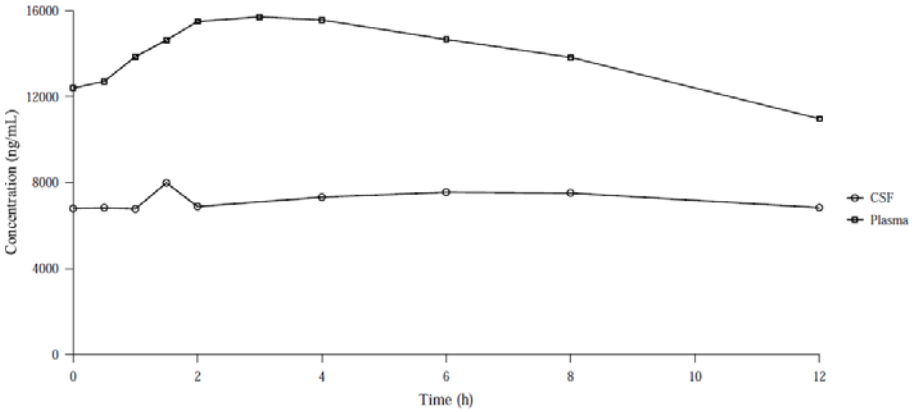


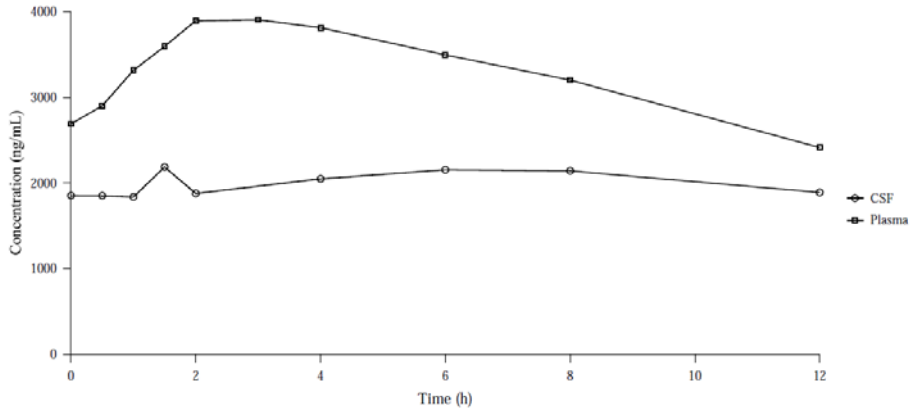
Point estimates and 90% confidence intervals for the comparison of CSF versus plasma pharmacokinetic parameters of BIA 2-194 following oral administration of OXC 600 mg b.i.d. are summarized below:

BIA 2-194 - CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	46.81 40.43; 54.20
AUC_{0-12} (ng.h/mL)	PE (%) 90% CI	52.32 44.74; 61.19

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

BIA 2-195 (L-licabazepine):

Mean plasma versus CSF BIA 2-195 concentration-time profile on Day 9 following oral administration of OXC 600 mg b.i.d. is shown below:



Point estimates and 90% confidence intervals for the comparison of CSF versus plasma pharmacokinetic parameters of BIA 2-195 following oral administration of OXC 600 mg b.i.d. are summarized below:

Reference ID: 3374277

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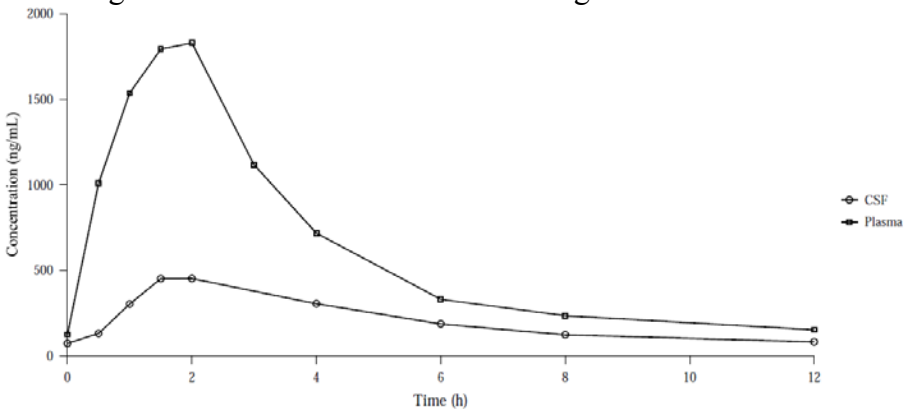
BIA 2-195 - CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	53.14 45.82; 61.63
AUC_{0-12} (ng.h/mL)	PE (%) 90% CI	61.48 52.29; 72.27

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0111) were found.

OXC:

Mean plasma versus CSF OXC concentration-time profile on Day 9 following oral administration of OXC 600 mg b.i.d. is shown below:



Point estimates and 90% confidence intervals for the comparison of CSF versus plasma pharmacokinetic parameters of OXC following oral administration of OXC 600 mg b.i.d. are summarized below:

OXC - CSF/plasma		
C_{max} (ng/mL)	PE (%) 90% CI	22.51 16.24; 31.19
AUC_{0-12} (ng.h/mL)	PE (%) 90% CI	34.83 27.23; 44.55

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0727) were found.

<u>Comparison of plasma and CSF PK profiles between treatment groups (ESL vs., OXC)</u>

Plasma Matrix:

BIA 2-194 (S-licabazepine):

Mean plasma BIA 2-194 concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are shown below, respectively:

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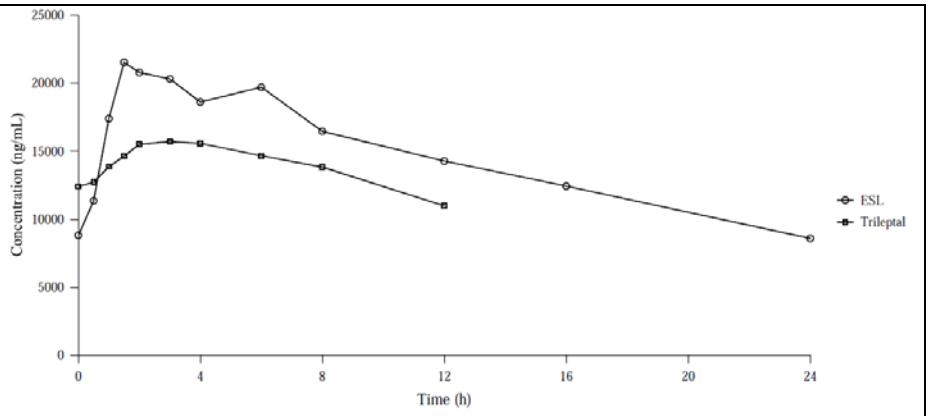
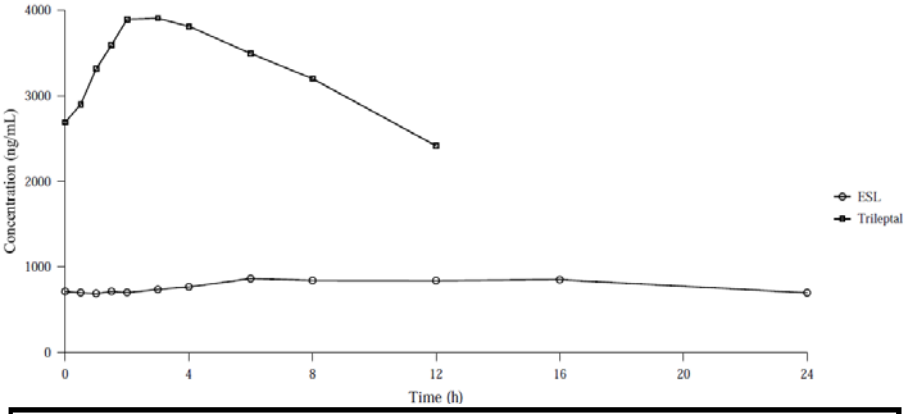


BIA 2-194 - OXC/ESL treatment		
C_{max} (ng/mL)	PE (%) 90% CI	67.53 54.46; 83.75
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	96.86 80.60; 116.41

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

BIA 2-195 (L-licabazepine):

Mean plasma BIA 2-195 concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are shown below, respectively:



BIA 2-195 – OXC/ESL treatment		
C_{max} (ng/mL)	PE (%) 90% CI	455.84 374.80; 554.39
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	416.51 342.87; 505.97

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0468) were found.

OXC:

Mean plasma OXC concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are shown below, respectively:

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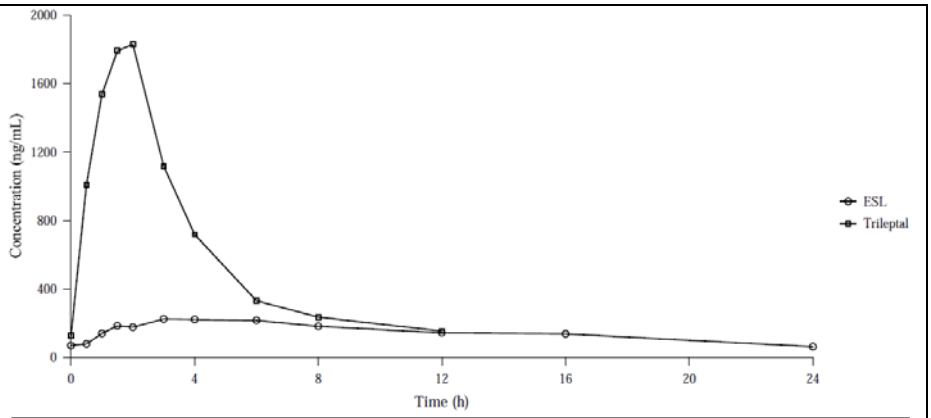


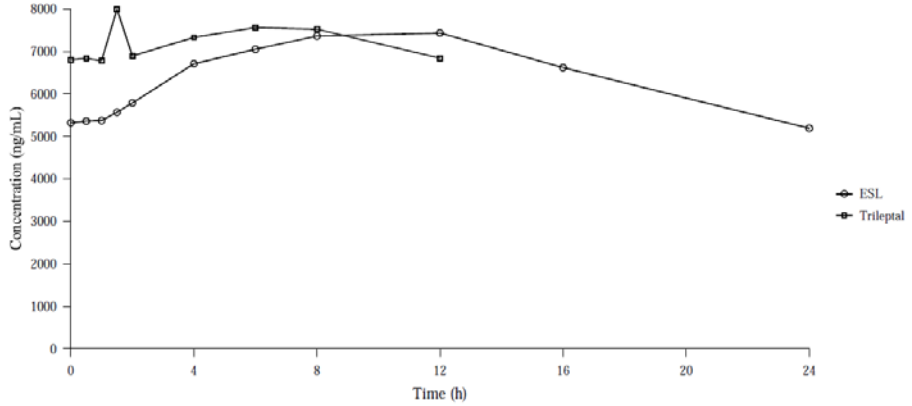
OXC - OXC/ESL treatment		
C_{max} (ng/mL)	PE (%) 90% CI	811.40 595.78; 1105.06
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	411.32 325.40; 519.94

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0315) were found.

CSF Matrix:

BIA 2-194 (S-licabazepine):

Mean CSF BIA 2-194 concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are shown below, respectively:



BIA 2-194 - OXC/ESL treatment		
C_{max} (ng/mL)	PE (%) 90% CI	100.09 87.79; 114.13
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	111.56 98.02; 126.97

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

BIA 2-195 (L-licabazepine):

Mean CSF BIA 2-195 concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are

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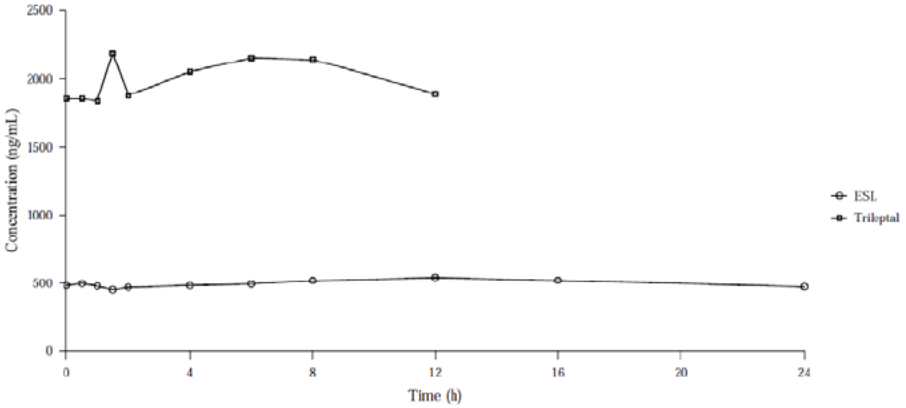
shown below, respectively:

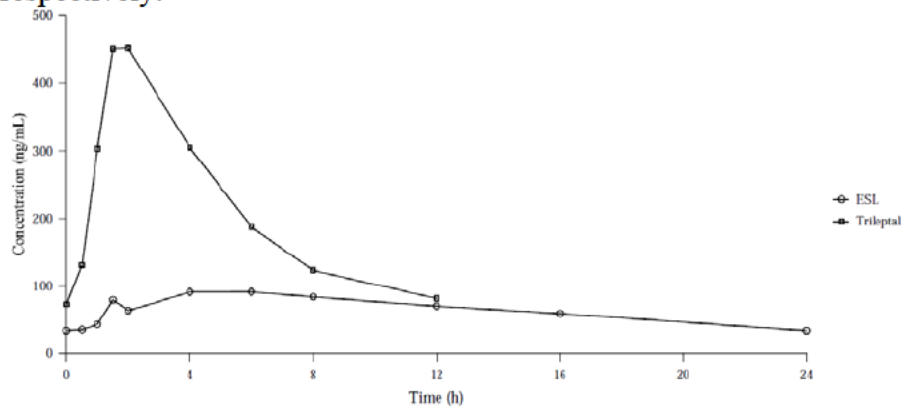


BIA 2-195 - OXC/ESL		
C_{max} (ng/mL)	PE (%) 90% CI	398.64 320.42; 495.96
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	407.04 331.75; 499.42

PE = point estimate; CI = confidence interval
No differences on t_{max} were found.

OXC

Mean CSF OXC concentration-time profiles and point estimates with 90% CI for the PK comparison on Day 9 following oral administration of ESL 1200 mg q.d. versus OXC 600 mg b.i.d. are shown below, respectively:



OXC – OXC/ESL		
C_{max} (ng/mL)	PE (%) 90% CI	480.54 366.23; 630.54
AUC_{0-24} (ng.h/mL)	PE (%) 90% CI	326.61 272.67; 391.22

PE = point estimate; CI = confidence interval
Differences on t_{max} (p=0.0129) were found.

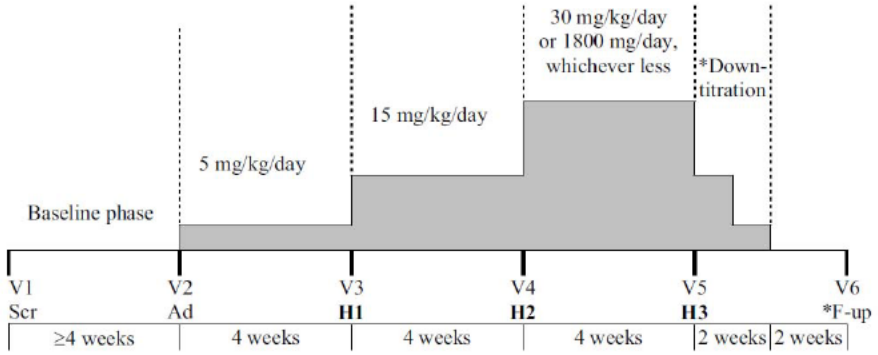
Safety	There was no SAE or death in the study.
Conclusion	Following ESL administration, the extent of plasma exposure to BIA 2-194, BIA 2-195 and OXC was 94%, 5% and 1%, respectively. The extent of CNS exposure to BIA 2-194, BIA 2-195 and OXC was 92%, 7% and 1%, respectively; Following OXC administration, the extent

	of plasma exposure to BIA 2-194, BIA 2-195 and OXC was 78%, 18% and 3%, respectively. The extent of CNS exposure to BIA 2-194, BIA 2-195 and OXC was 76%, 21% and 2%, respectively. Less than 50% of plasma BIA 2-194 and OXC can be found in CNS and this in both treatments. Although a slightly higher ratio was observed for BIA 2-195 (53 to 61%), the same parallelism was found for BIA 2-195 and this seemed to be independent of the parent compound administered (ESL or OXC). No lag time was observed independently of biological matrix (plasma or CSF) or treatment (ESL or OXC) considered. However, a small delay was observed in CSF tmax in comparison with plasma tmax. *Less fluctuation of BIA 2-194 concentration from peak to trough in CSF than in plasma was observed in ESL (41% v.s., 113%) and OXC (14% v.s., 39%) treatment groups; less fluctuation of OXC concentration from peak to trough in CSF than in plasma was observed in ESL (99% v.s., 133%) and OXC (182% v.s., 315%) treatment groups, in which OXC treatment group was more pronounced. Due to the limited sampling time (up to 24 hours for ESL treatment group and 12 hours for OXC treatment group), the estimated t1/2 values for BIA 2-194 is not reliable.*

PK in Pediatric Patients

Study **BIA-2093-202**	Pharmacokinetics, efficacy and tolerability of BIA 2-093 in children and adolescents with refractory partial epilepsy.
Principal Investigator	Dr. Ioana Minciu
Study Center	Clinica de Neurologie Pediatrica, Spitalul "Alexandru Obregia", Soseaua Berceni nr.10, sect.4, 041914, Bucharest, Romania.
Study Period	6/15/05 – 4/17/06
Study Objective	The primary trial objective was to characterize the PK of eslicarbazepine acetate in children and adolescents with epilepsy. The secondary objectives were: • To assess the efficacy of eslicarbazepine acetate as add-on therapy in children and adolescents with partial epilepsy. • To assess the tolerability of eslicarbazepine acetate as add-on therapy in children and adolescents with partial epilepsy.
Study Design and Dose Administration	This clinical study was planned to be performed as an open-label, single-center, multiple-dose study, in 30 pediatric 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 design flow chart is shown below:

Reference ID: 3374277

	 V - Visit; H - Hospitalisation; Scr - Screening; Ad - Admission to the treatment phase; F-up - Follow-up visit. * – Down-titration phase and follow-up visit were performed only in patients not continuing into compassionate use of Eslicarbazepine acetate. The study was constituted by a 4-week baseline phase, followed by 3 consecutive 4-week treatment periods with eslicarbazepine acetate in which patients received eslicarbazepine acetate 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). For Group 1 (2–6 years), oral suspension 50 mg/mL was used. The dose was to be rounded to the nearest 25 mg unit. For Group 2 (7–11 years) and Group 3 (12–17 years), eslicarbazepine acetate strengths 200 mg, 400 mg, 600 mg and 800 mg tablets might be used. The dose was to be rounded to the nearest 100 mg unit. Half tablets might be used for dosage adjustment (tablets were scored). After the last treatment period or in the event of premature discontinuation, the dose had to be down-titrated during a 2-week period. After the last treatment period patient could continue receiving eslicarbazepine acetate ("compassionate use") if both parent(s)/ guardian(s)/ patient and his/her physician agreed this was in the best patient's interest. *Reviewer's comments: there was no food-taking information in the study report. Since food has no effect on the PK of eslicarbazepine after oral administration of ESL, this is not a major concern for the PK result.*
Study Population	Planned: 30 patients (10 patients per age group: Group 1 = 2-6 years; Group 2 = 7-11 years; Group 3 = 12-17 years). Analyzed: 29 Caucasian patients in Pharmacokinetic and Efficacy populations (Group 1: n=11, 3M/8F; Group 2: n=8, 2M/6F; Group 3: n=10, 7M/3F); 31 patients in Safety population (Group 1: n=12; Group 2: n=8; Group 3: n=11). The mean values of body weight for each group are: 16.9 kg (Group 1), 29.9 kg (Group 2), and 49.8 kg (Group 3). Two patients [one from the age Group 1 (2-6 yrs) and one from the age Group 3 (12-17 yrs)] discontinued the study during the first (5 mg/kg/day) treatment period; 29 patients finished at least one treatment period, have valid pharmacokinetic/patient diary data for

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<table>
<tr><td></td><td>that treatment period and, therefore, were included into the PK and efficacy population for a given treatment period; 26 patients completed all three treatment periods.</td></tr>
<tr><td>Investigational Product</td><td>
<table>
<tr><th>Eslicarbazepine acetate</th><th>Batches numbers</th><th>Expiry date</th></tr>
<tr><td>200 mg tablets</td><td>#040142-L</td><td>December 2006</td></tr>
<tr><td>400 mg tablets</td><td>#040120-L</td><td>March 2007</td></tr>
<tr><td>600 mg tablets</td><td>#040121-L</td><td>March 2007</td></tr>
<tr><td>800 mg tablets</td><td>#050032-L</td><td>April 2008</td></tr>
<tr><td>50 mg/mL oral suspension</td><td>#040144-L</td><td>January 2007</td></tr>
</table>
Reviewer's Comments: relative BA has been established for three formulations: 2 clinical trial tablet formulation oral suspension 50 mg/ml (test 1), tablet strength 200 mg (test 2), and tablet strength 800 (reference). Please refer to Section 2.5.3 of Dr. Tandon's review in DARRTS. However, this 200 mg tablet is not the to-be-marketed tablet.
</td></tr>
<tr><td>Sampling: Blood</td><td>Blood samples (2.5mL each) for the plasma assay of eslicarbazepine acetate and its metabolites were taken during the hospitalizations (H1, H2, and H3) at weeks 4, 8 and 12 at the following times: pre-dose, and 0.5, 1.5, 3, 4.5, 6 and 12 hours post-dose.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Bioanalysis</td><td>Sample analysis was carried out at (b) (4) using a previously validated method using solid phase extraction followed by HPLC analysis on a mass spectrometer (chiral LC-MS/MS) between 2/6/2006 and 12/8/2006.
<table>
<tr><th></th><th>BIA 2-093 (parent)</th><th>BIA 2-194 (eslicarbazepine)</th><th>BIA 2-195 (R-licarbazepine)</th><th>OXC</th></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>50 - 1000</td><td>50 - 25000</td><td>50 - 25000</td><td>50 - 1000</td></tr>
<tr><td>LLOQ</td><td>50 ng/ml</td><td>50 ng/ml</td><td>50 ng/ml</td><td>50 ng/ml</td></tr>
<tr><td>QCs (ng/ml)</td><td>50, 140, 400, 800.</td><td>50, 140, 10000, 20000.</td><td>50, 140, 10000, 20000.</td><td>50, 140, 400, 800.</td></tr>
<tr><td>Inter-run precision</td><td>3% - 4%</td><td>2.6% - 8.6%</td><td>2.8% - 7.2%</td><td>4.1% - 6.8%</td></tr>
<tr><td>Inter-run accuracy</td><td>96.1% - 104.9%</td><td>97.6% - 106.1%</td><td>86.7% - 106.4%</td><td>93.1% - 112.2%</td></tr>
</table>
Quality control assay validation is acceptable.</td></tr>
<tr><td>PK Assessment</td><td>PK parameters of eslicarbazepine acetate and metabolites BIA 2-194 and BIA 2-195 were derived from the concentration versus time profiles post last dose of each 4-week treatment period with a different dosage regimen: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-inf}}$, CLss/F.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG, Brain CT scan or MRI, Clinical laboratory, and AEs.</td></tr>
<tr><td>PD Assessment (efficacy)</td><td>Percentage change in seizure frequency during each 4-week treatment period compared to the baseline phase; percentage of patients who</td></tr>
</table>

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	became seizure-free.
Concomitant Medications	Doses of 1 to 3 concomitant AEDs (other than OXC and CBZ) were kept stable from 1 month prior to enrolment into the baseline phase and throughout the study, unless clinically unacceptable. The additional use of benzodiazepines for prolonged or iterative seizures was allowed if not more frequent than 2 times per week (unless used as one of the concomitant AEDs). In total, 17 patients (58.6%) of the PKP and EP populations were taking concomitant medication for conditions other than epilepsy during the study; most of them belonged to Group 1 (n=9, 81.8%). The mostly used non-epileptic drugs were ibuprofen (24% of patients) and paracetamol (21%). Concomitant AEDs are listed below:
Pharmacokinetic Results	Neither mean nor individual plasma concentrations versus time profiles were displayed for BIA 2-093 (parent drug) because plasma levels were systematically below the limit of quantification (50ng/mL) at all sampling times. <u>PK profiles of BIA 2-194, 2-195, and OXC in Group 1 (2–6 years) at three dose levels</u>:

ATC 2nd level PT name	Age group (yrs) 2–6	7–11	12–17	Total
Total Number of Patients in EP	11	8	10	29
Number of Patients with Concomitant AED medication	11 (100.0%)	8 (100.0%)	10 (100.0%)	29 (100.0%)
Concomitant Medication				
ANTIEPILEPTICS	11 (100%)	8 (100%)	10 (100%)	29 (100%)
LAMOTRIGINE	7 (64%)	4 (50%)	8 (80%)	19 (66%)
VALPROIC ACID	8 (73%)	5 (63%)	6 (60%)	19 (66%)
TOPIRAMATE	5 (45%)	5 (63%)	4 (40%)	14 (48%)
CLONAZEPAM	2 (18%)	2 (25%)	4 (40%)	8 (28%)
PHENOBARBITAL	2 (18%)	2 (25%)	0	4 (14%)
GABAPENTIN	1 (9%)	1 (13%)	1 (10%)	3 (10%)
OXCARBAZEPINE	1 (9%)	0	0	1 (3%)
PHENYTOIN	1 (9%)	0	0	1 (3%)
PSYCHOLEPTICS	0	2 (25%)	0	2 (7%)
DIAZEPAM	0	1 (13%)	0	1 (3%)
NITRAZEPAM	0	1 (13%)	0	1 (3%)

Notes: Concomitant medications include all medications taken after the start of study treatment and all medications taken prior to the start of study treatment but continued to be taken after start of study treatment;
Anti-epileptic drugs are defined according indication (AED1, AED2 or AED3) or ATC 2nd level ('ANTIEPILEPTIC').

Figure 3: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

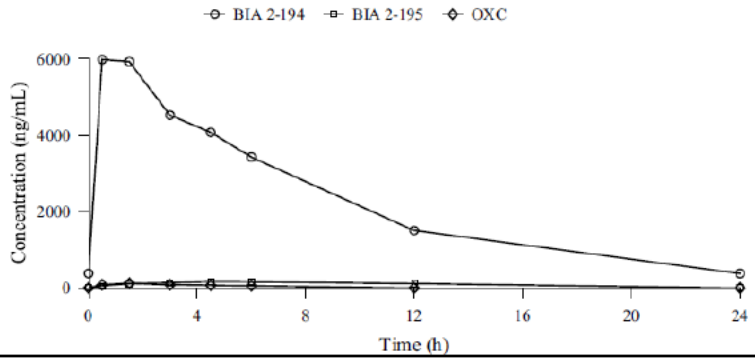

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Figure 4: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

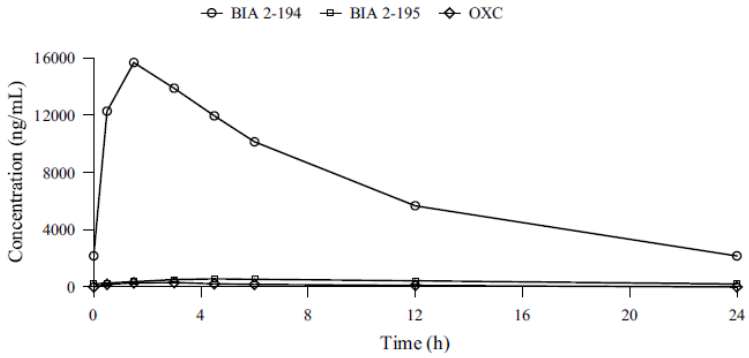
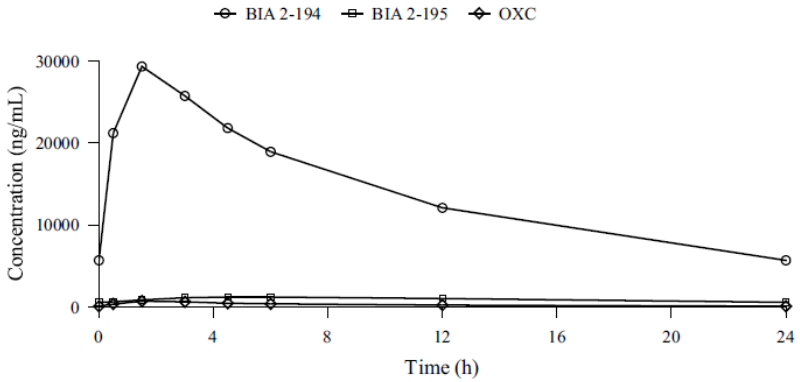


Figure 5: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]



PK parameters of BIA 2-194 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 11: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	11	11	11	11	11	11	11
G_{mean}	6704	0.824	51769	54759	51769	5.36	96.6
A_{mean}	6921	0.955	53599	57073	53599	5.51	100
SD	1794	0.522	14351	16654	14351	1.36	29.2
CV(%)	25.9	54.7	26.8	29.2	26.8	24.8	29.1
Median	6494	0.50	54313	56936	54313	5.36	92.1
Minimum	4075	0.50	33263	34066	33263	4.00	67.7
Maximum	10002	1.50	73826	84137	73826	7.91	150

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 14: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	10	10	10	10
G_{mean}	15992	1.54	165085	189356	165085	7.86	90.9
A_{mean}	16183	1.70	169925	198089	169925	8.07	93.6
SD	2609	0.753	42671	62876	42671	1.97	24.1
CV(%)	16.1	44.3	25.1	31.7	25.1	24.4	25.8
Median	16103	1.50	170433	193397	170433	7.96	88.5
Minimum	13018	0.50	109138	112735	109138	4.99	60.9
Maximum	19706	3.00	246380	324092	246380	11.4	137

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 17: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	9	9	9	9	9	9	9
G_{mean}	29578	1.33	330408	411057	330408	9.84	90.8
A_{mean}	29935	1.39	339387	431533	339387	10.2	93.8
SD	4627	0.333	76600	130594	76600	2.65	28.0
CV(%)	15.5	24.0	22.6	30.3	22.6	26.0	29.9
Median	30783	1.50	343852	392432	343852	10.2	87.2
Minimum	20359	0.50	185659	194659	185659	5.42	68.1
Maximum	34791	1.50	440482	603101	440482	12.9	162

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK parameters of BIA 2-195 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 21: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	11	11	11	8	11	8	11
G_{mean}	173	4.64	1913	3776	2370	10.5	2110
A_{mean}	182	4.91	2195	4108	2546	11.5	2247
SD	58.7	1.36	1294	1844	1096	5.38	802
CV(%)	32.3	27.6	59.0	44.9	43.1	46.6	35.7
Median	178	4.50	1829	3701	2414	11.4	2072
Minimum	91.3	1.50	907	1938	1365	5.51	946
Maximum	291	6.00	5285	7443	5285	21.0	3664

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 24: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	9	10	9	10
G_{mean}	570	5.05	9024	13277	9024	13.0	1662
A_{mean}	607	5.40	9493	14891	9493	14.2	1733
SD	238	2.47	3587	9311	3587	5.93	494
CV(%)	39.2	45.7	37.8	62.5	37.8	41.7	28.5
Median	527	4.50	9095	11857	9095	14.0	1650
Minimum	339	3.00	5906	7317	5906	5.07	799
Maximum	1072	12.0	18766	38751	18766	25.2	2540

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 27: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	9	9	9	8	9	8	9
G_{mean}	1231	5.45	21474	32153	21474	15.2	1397
A_{mean}	1270	5.83	22408	35669	22408	17.1	1455
SD	328	2.54	7207	18584	7207	8.79	434
CV(%)	25.8	43.5	32.2	52.1	32.2	51.3	29.9
Median	1172	6.00	20508	30254	20508	14.2	1463
Minimum	754	3.00	13029	18857	13029	5.86	794
Maximum	1862	12.0	37803	72795	37803	32.4	2303

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK parameters of OXC following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 30: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	11	11	11	8	11	8	11
G_{mean}	121	1.48	516	1423	701	6.89	7135
A_{mean}	137	1.73	648	1512	874	8.41	9660
SD	76.0	0.905	401	538	516	5.53	8874
CV(%)	55.4	52.4	61.8	35.6	59.1	65.8	91.9
Median	105	1.50	630	1600	889	7.41	5624
Minimum	61.5	0.50	130	847	169	2.08	3041
Maximum	300	3.00	1323	2292	1644	19.5	29656

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 33: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	10	10	10	10
G_{mean}	316	2.37	2282	3446	2845	7.31	5273
A_{mean}	352	2.55	2468	3632	2994	8.09	5519
SD	178	1.01	1134	1270	1063	3.66	1653
CV(%)	50.6	39.7	46.0	35.0	35.5	45.2	30.0
Median	268	3.00	2020	3459	2535	8.24	5918
Minimum	156	1.50	1440	1981	1909	3.09	2921
Maximum	710	4.50	5136	6086	5136	14.3	7859

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 36: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 1 (2-6 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	9	9	9	9	9	9	9
G_{mean}	724	1.95	6230	7580	6526	7.80	4597
A_{mean}	769	2.39	6523	8044	6757	8.17	4740
SD	289	1.62	2192	3248	1992	2.96	1155
CV(%)	37.6	67.6	33.6	40.4	29.5	36.2	24.4
Median	606	1.50	5600	6209	5718	8.05	5246
Minimum	442	0.50	4286	5861	5160	4.91	2878
Maximum	1274	6.00	10423	15177	10423	15.3	5814

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK profiles of BIA 2-194, 2-195, and OXC in Group 2 (7–11 years) at three dose levels:

Figure 6: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

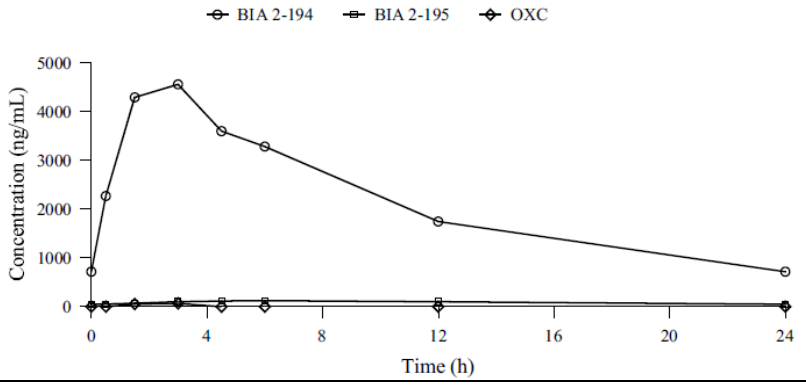

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Figure 7: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

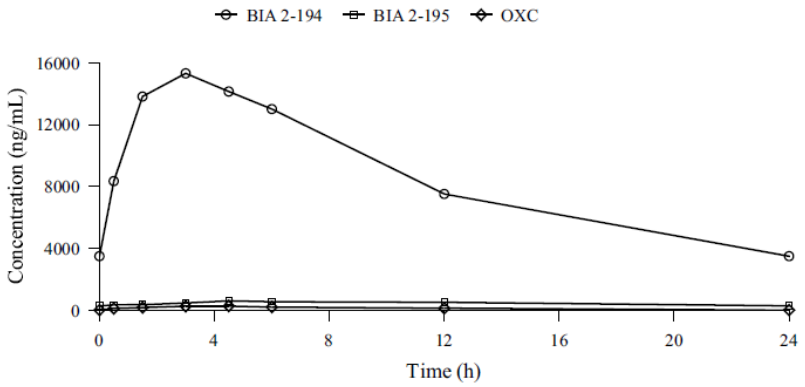
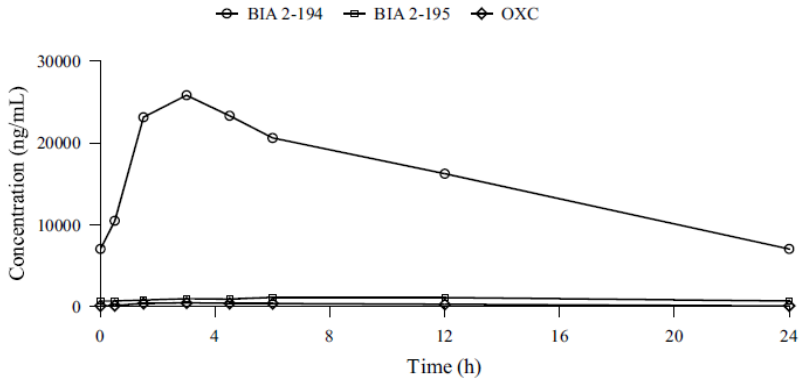


Figure 8: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]



PK parameters of BIA 2-194 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 12: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	8	8	8	8
G_{mean}	4525	1.85	48154	55415	48154	7.73	104
A_{mean}	4820	2.13	51748	61012	51748	7.87	112
SD	1693	0.991	21492	30846	21492	1.76	46.5
CV(%)	35.1	46.6	41.5	50.6	41.5	22.3	41.7
Median	4612	2.25	45520	52847	45520	7.12	110
Minimum	1985	0.50	23918	26048	23918	6.65	53.2
Maximum	7554	3.00	93919	128229	93919	12.0	209

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 15: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	8	8	8	8
G_{mean}	16005	2.89	202472	250811	202472	9.54	74.1
A_{mean}	16395	3.00	206080	256646	206080	9.66	75.5
SD	3680	0.802	39829	55796	39829	1.68	16.5
CV(%)	22.4	26.7	19.3	21.7	19.3	17.3	21.9
Median	16677	3.00	214770	256730	214770	9.50	69.8
Minimum	10214	1.50	137320	154190	137320	7.24	57.1
Maximum	21659	4.50	262575	342043	262575	12.4	109

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 18: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	7	7	7	7	7	7	7
G_{mean}	25997	2.61	368353	494552	368353	11.3	81.4
A_{mean}	26890	2.79	378259	507645	378259	11.9	84.1
SD	6944	1.04	85989	117245	85989	3.97	24.7
CV(%)	25.8	37.2	22.7	23.1	22.7	33.3	29.4
Median	25844	3.00	411447	539193	411447	11.1	72.9
Minimum	14719	1.50	225506	313261	225506	5.73	64.3
Maximum	34871	4.50	466863	637887	466863	17.9	133

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK parameters of BIA 2-195 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 22: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	6	8	6	8
G_{mean}	124	5.58	1866	3529	2049	15.9	2440
A_{mean}	126	6.00	2075	3712	2163	16.4	2612
SD	25.5	2.66	827	1118	670	4.04	1123
CV(%)	20.2	44.3	39.9	30.1	31.0	24.7	43.0
Median	134	6.00	2473	3905	2473	17.1	2023
Minimum	90.8	3.00	742	1723	1096	11.5	1827
Maximum	156	12.0	2736	4862	2736	22.0	4563

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 25: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	7	8	7	8
G_{mean}	628	5.47	9872	21403	10448	21.3	1436
A_{mean}	647	5.81	10355	22922	10671	23.3	1470
SD	176	2.59	2889	9041	2201	10.4	363
CV(%)	27.2	44.6	27.9	39.4	20.6	44.5	24.7
Median	604	4.50	11032	18940	11032	18.5	1361
Minimum	421	4.50	4393	12308	6919	13.4	1152
Maximum	1007	12.0	13026	36382	13026	36.5	2168

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 28: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	7	7	7	4	7	4	7
G_{mean}	1159	7.31	21327	54099	21327	22.5	1407
A_{mean}	1239	7.71	22941	56419	22941	23.1	1542
SD	461	2.93	8629	20055	8629	6.28	806
CV(%)	37.2	38.0	37.6	35.5	37.6	27.2	52.3
Median	1278	6.00	23188	50020	23188	22.95	1294
Minimum	595	6.00	9218	40052	9218	17.43	827
Maximum	1801	12.0	36270	85585	36270	29.14	3255

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK parameters of OXC following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 31: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	7	7	7	2	7	2	7
G_{mean}	89.0	3.00	238	-	397	-	12580
A_{mean}	91.8	3.43	311	-	495	-	17829
SD	25.7	1.88	177	-	261	-	18240
CV(%)	28.0	54.8	56.9	-	52.8	-	102
Median	86.3	3.00	363	-	625	-	8005
Minimum	61.6	1.50	37	-	92.4	-	6664
Maximum	140	6.00	556	-	750	-	54127

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 34: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	6	8	6	8
G_{mean}	277	3.81	2476	4724	2862	10.2	5241
A_{mean}	296	3.94	2888	4859	3184	10.9	6080
SD	112	1.12	1521	1175	1359	4.09	4206
CV(%)	37.8	28.3	52.7	24.2	42.7	37.6	69.2
Median	298	3.75	2484	5144	3111	10.0	4881
Minimum	137	3.00	748	2974	944	5.71	3018
Maximum	482	6.00	4969	6054	4969	17.7	15895

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 37: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 2 (7-11 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	7	7	7	7	7	7	7
G_{mean}	471	3.72	5848	7927	6105	9.93	4914
A_{mean}	489	3.86	6154	8094	6301	10.8	5078
SD	145	1.18	1943	1807	1680	5.01	1422
CV(%)	29.6	30.6	31.6	22.3	26.7	46.4	28.0
Median	482	3.00	5676	8205	5676	8.29	5286
Minimum	318	3.00	2942	6322	3974	6.43	3593
Maximum	717	6.00	8350	11140	8350	19.8	7548

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK profiles of BIA 2-194, 2-195, and OXC in Group 3 (12–17 years) at three dose levels:

Figure 9: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

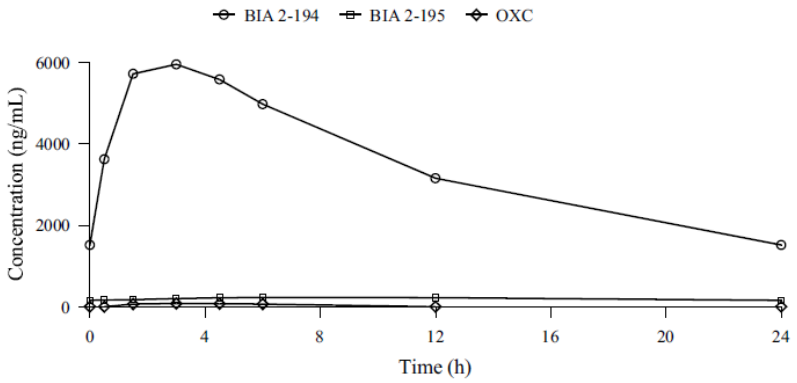

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Figure 10: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

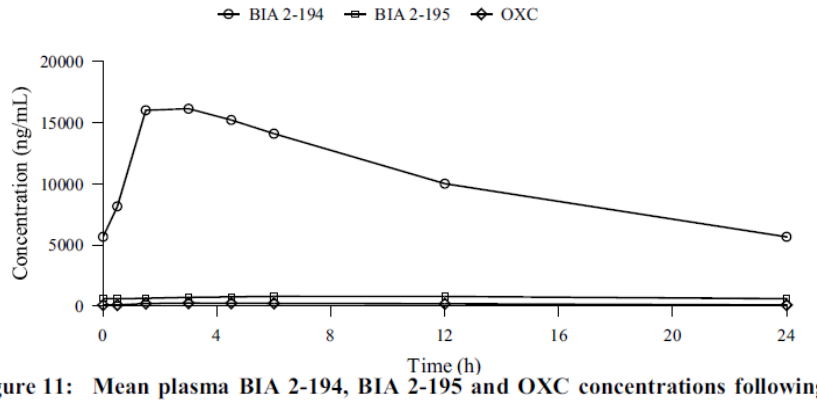
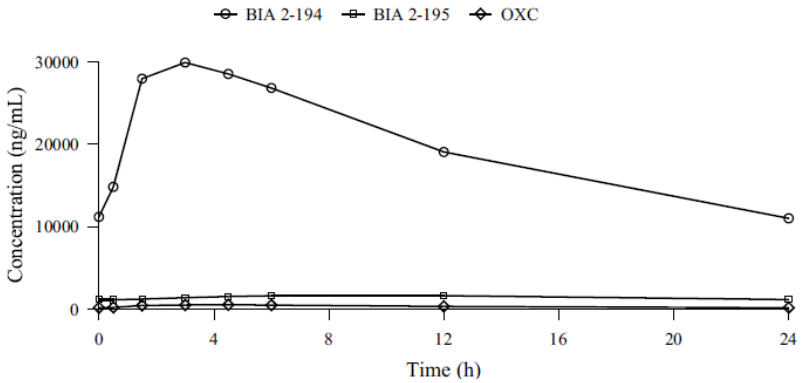


Figure 11: Mean plasma BIA 2-194, BIA 2-195 and OXC concentrations following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]



PK parameters of BIA 2-194 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 13: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	10	10	10	10
G_{mean}	6173	1.90	81416	104267	81416	10.4	61.4
A_{mean}	6382	2.15	83691	108436	83691	10.6	63.1
SD	1854	0.944	20997	31143	20997	2.41	15.5
CV(%)	29.0	43.9	25.1	28.7	25.1	22.7	24.6
Median	5654	2.25	76581	103528	76581	9.43	65.5
Minimum	4344	0.50	52806	61600	52806	8.17	39.6
Maximum	10559	3.00	126253	148504	126253	14.1	94.7

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 16: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	10	10	10	10
G_{mean}	16882	2.12	245897	357439	245897	13.6	61.0
A_{mean}	17194	2.25	251638	374430	251638	14.1	62.5
SD	3410	0.791	54972	116140	54972	4.07	15.4
CV(%)	19.8	35.1	21.8	31.0	21.8	28.9	24.7
Median	17365	2.25	259464	372119	259464	12.3	57.9
Minimum	12143	1.50	155636	195023	155636	10.2	43.4
Maximum	21920	3.00	345834	536640	345834	22.7	96.4

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 19: Pharmacokinetic parameters of BIA 2-194 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	8	8	8	8
G_{mean}	31987	2.65	471570	714563	471570	14.6	63.4
A_{mean}	32400	3.00	476183	730724	476183	15.1	64.0
SD	6005	1.60	70624	156745	70624	4.38	9.85
CV(%)	18.5	53.5	14.8	21.5	14.8	29.0	15.4
Median	30744	3.00	481801	729084	481801	14.2	62.2
Minimum	26547	1.50	382488	467787	382488	9.19	50.1
Maximum	46445	6.00	598735	918437	598735	21.7	78.4

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; Coefficient of variation

PK parameters of BIA 2-195 following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 23: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 5 mg/kg/day BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	6	10	6	10
G_{mean}	224	7.69	4584	13107	4584	32.5	1091
A_{mean}	234	8.25	4808	16095	4808	36.5	1142
SD	70.8	3.26	1593	11143	1593	19.2	361
CV(%)	30.3	39.5	33.1	69.2	33.1	52.6	31.6
Median	222	6.00	4434	11643	4434	30.6	1132
Minimum	151	4.50	2892	6550	2892	17.2	623
Maximum	362	12.0	8031	30096	8031	65.2	1729

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 26: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	7	10	7	10
G_{mean}	796	6.89	16632	46101	16632	38.2	902
A_{mean}	820	7.50	17243	55801	17243	43.8	930
SD	228	3.24	5313	42541	5313	26.3	224
CV(%)	27.8	43.2	30.8	76.2	30.8	60.1	24.1
Median	749	6.00	15192	35405	15192	38.4	987
Minimum	581	3.00	11989	25823	11989	21.5	508
Maximum	1358	12.0	29538	142136	29538	93.6	1251

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 29: Pharmacokinetic parameters of BIA 2-195 following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	2	8	2	8
G_{mean}	1636	10.09	34463	-	34463	-	867
A_{mean}	1648	10.50	34643	-	34643	-	871
SD	218	2.78	3880	-	3880	-	86.7
CV(%)	13.2	26.5	11.2	-	11.2	-	10.0
Median	1588	12.0	34693	-	34693	-	865
Minimum	1391	6.00	30799	-	30799	-	706
Maximum	2066	12.0	42492	-	42492	-	968

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

PK parameters of OXC following a 4-week QD dosing of 5, 15, or 30 mg/kg/day are presented below, respectively:

Table 32: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	3	10	3	10
G_{mean}	96.8	3.78	464	2033	683	10.1	7326
A_{mean}	100	4.05	677	2174	878	11.6	9712
SD	24.4	1.42	544	1024	581	7.84	7565
CV(%)	24.5	35.1	80.4	47.1	66.1	67.4	77.9
Median	100	4.50	660	1633	810	8.35	6312
Minimum	63.0	1.50	141	1535	214	5.97	2893
Maximum	133	6.00	1728	3356	1728	20.6	23414

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

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Table 35: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	10	10	10	10	10	10	10
G_{mean}	253	3.04	3749	5654	3872	13.1	3874
A_{mean}	259	3.30	3969	6172	4041	14.0	4038
SD	58.7	1.38	1370	3026	1264	5.51	1215
CV(%)	22.6	41.8	34.5	49.0	31.3	39.3	30.1
Median	274	3.00	4010	5402	4010	11.8	3751
Minimum	163	1.50	1890	3450	2552	7.92	2261
Maximum	329	6.00	6634	12603	6634	22.22	5877

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Table 38: Pharmacokinetic parameters of OXC following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 [Group 3 (12-17 yrs)]

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{τ} (ng.h/mL)	$t_{1/2}$ (h)	CLss/F (mL/h/kg)
n	8	8	8	8	8	8	8
G_{mean}	557	3.49	7954	10703	7954	11.6	3756
A_{mean}	566	3.94	8025	10867	8025	11.8	3793
SD	109	1.78	1123	1989	1123	2.54	572
CV(%)	19.2	45.2	14.0	18.3	14.0	21.5	15.1
Median	554	4.50	8252	10722	8252	11.7	3609
Minimum	429	1.50	6291	7783	6291	8.83	3177
Maximum	781	6.00	9442	13752	9442	15.0	4769

n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

As it's seen in adults, BIA 2-194 is the major metabolite and that BIA 2-195 and OXC are minor metabolites in pediatric patients.
Dose-proportionality of BIA 2-194 was observed in all age groups.
Reviewer's comments: due to the limited LLOQ (50 ng/ml) for BIA-195 and OXC, the estimated values of AUC for both analytes are not reliable.

Cross-group PK comparisons:
BIA 2-194:

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Figure 12: Individual plasma BIA 2-194 concentration-time profiles following a 4-week repeated once-daily oral administration of 5 mg/kg/day BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

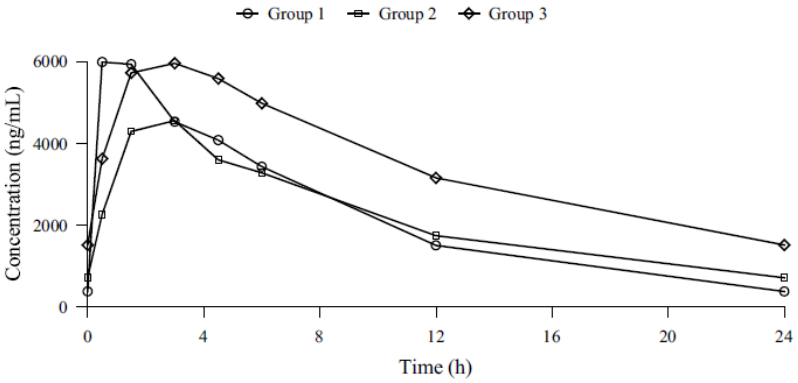

Figure 13: Individual plasma BIA 2-194 concentration-time profiles following a 4-week repeated once-daily oral administration of 15 mg/kg/day BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

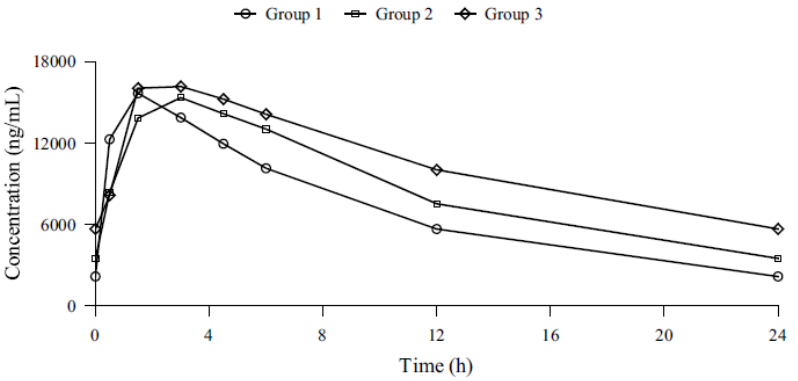

Figure 14: Individual plasma BIA 2-194 concentration-time profiles following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

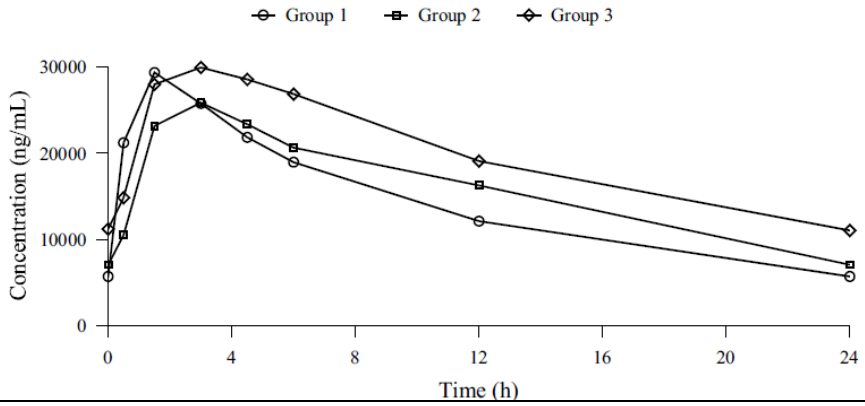

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Table 20: Arithmetic mean±SD pharmacokinetic parameters of BIA 2-194 following once-daily administration of BIA 2-093 5 mg/kg/day, 15 mg/kg/day and 30 mg/kg/day to epileptic children aged 2-6 years (Group 1), 7-11 years (Group 2) and 12-17 years (Group 3)

	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	6921	1	53599	57073	53599	6	100
(2-6 yrs)	1794	1	14351	16654	14351	1	29
Group 2	4820	2	51748	61012	51748	8	112
(7-11 yrs)	1693	1	21492	30846	21492	2	47
Group 3	6382	2	83691	108436	83691	11	63
(12-17 yrs)	1854	1	20997	31143	20997	2	16
Dosage regimen 15 mg/kg/day							
Group 1	16183	2	169925	198089	169925	8	94
(2-6 yrs)	2609	1	42671	62876	42671	2	24
Group 2	16395	3	206080	256646	206080	10	76
(7-11 yrs)	3680	1	39829	55796	39829	2	17
Group 3	17194	2	251638	374430	251638	14	63
(12-17 yrs)	3410	1	54972	116140	54972	4	15
Dosage regimen 30 mg/kg/day							
Group 1	29935	1	339387	431533	339387	10	94
(2-6 yrs)	4627	0	76600	130594	76600	3	28
Group 2	26890	3	378259	507645	378259	12	84
(7-11 yrs)	6944	1	85989	117245	85989	4	25
Group 3	32400	3	476183	730724	476183	15	64
(12-17 yrs)	6005	2	70624	156745	70624	4	10

There was a dose-proportional dose increase in systemic exposure to BIA 2-194 with increasing doses on the three age groups:

Table 39: Relationship between the extent of systemic exposure to BIA 2-194 with increasing doses of BIA 2-093 in each age group

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

Fold increase in dosage or parameters between adjacent dosages
* Fold increase in dosage or parameter over the dose range 5 to 30 mg BIA 2-093
+ DPF = Dose proportionality factor = ratio of fold increase in parameter divided by fold increase in dosage

Systemic exposure of subjects from different age groups to BIA 2-194 exposed to a given dose of BIA 2-093 was estimated by calculating the geometric means ratios of Cmax and AUCτ:

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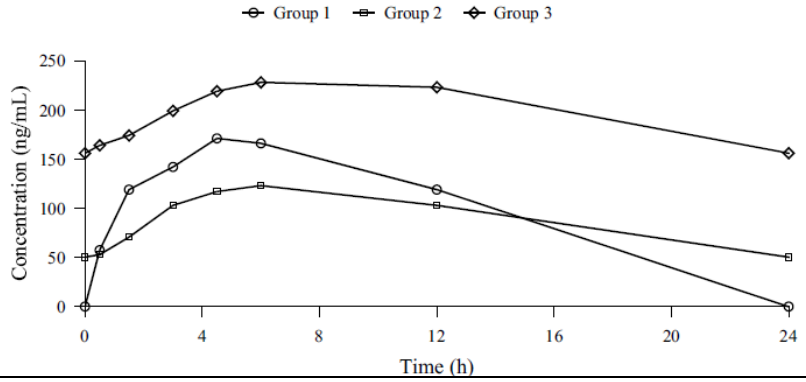
Table 40: **Geometric means ratio (GMR) of C_{max}, AUC and clearance pharmacokinetic parameters of BIA 2-194 following once-daily administration of BIA 2-093 5 mg/kg/day, 15 mg/kg/day and 30 mg/kg/day to epileptic children aged 2-6 years (Group 1), 7-11 years (Group 2) and 12-17 years (Group 3)**

Ratios	C_{max} GMR	AUC_{last} GMR	$AUC_{0-\infty}$ GMR	AUC_{τ} GMR	CLss/F GMR
5 mg/kg/day					
Group 1/Group 3	1.09	0.64	0.53	0.64	1.57
Group 2/Group 3	0.73	0.59	0.53	0.59	1.69
15 mg/kg/day					
Group 1/Group 3	0.95	0.67	0.53	0.67	1.49
Group 2/Group 3	0.95	0.82	0.70	0.82	1.21
30 mg/kg/day					
Group 1/Group 3	0.93	0.71	0.59	0.71	1.47
Group 2/Group 3	0.83	0.79	0.69	0.79	1.31

Reviewer's comments: the cross-group PK comparison is not acceptable, since different group has different concomitant medication profiles. For instance, 2 patients (18%) took phenobarbital in Group 1, 2 patients (25%) took phenobarbital in Group 2, but no patient took phenobarbital in Group 3. Phenobarbital increased BIA 2-194 CL/F by 11-31% and higher ESL dose may be needed.

BIA 2-195:

Figure 15: **Individual plasma BIA 2-195 concentration-time profiles following a 4-week repeated once-daily oral administration of 5 mg/kg/day BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)**



Reference ID: 3374277

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Figure 16: Individual plasma BIA 2-195 concentration-time profiles following a 4-week repeated once-daily oral administration of 15 mg/kg/day of BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

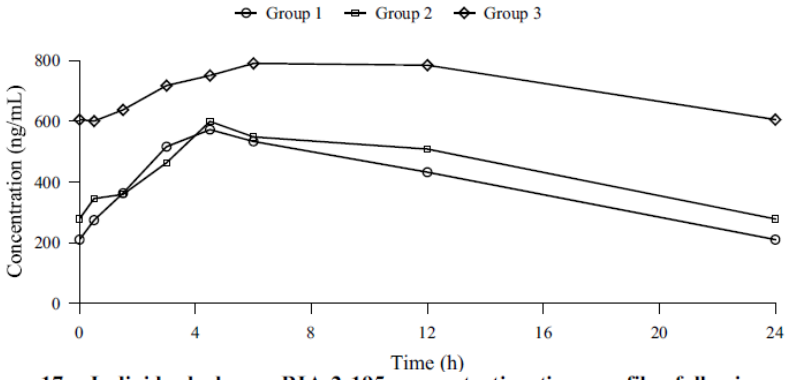
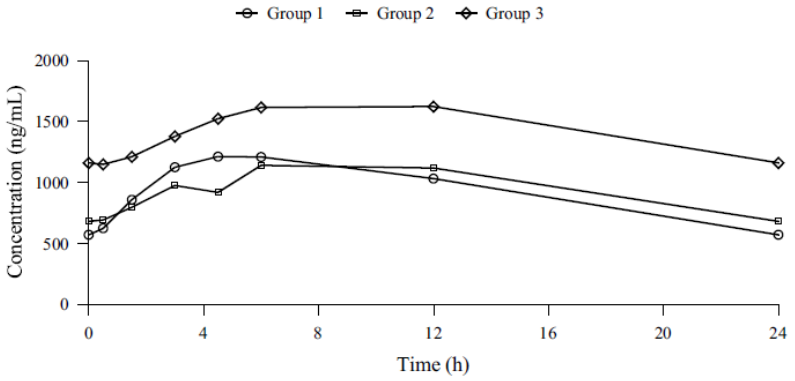


Figure 17: Individual plasma BIA 2-195 concentration-time profiles following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)



OXC:

Figure 18: Individual plasma OXC concentration-time profiles following a 4-week repeated once-daily oral administration of 5 mg/kg/day of BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

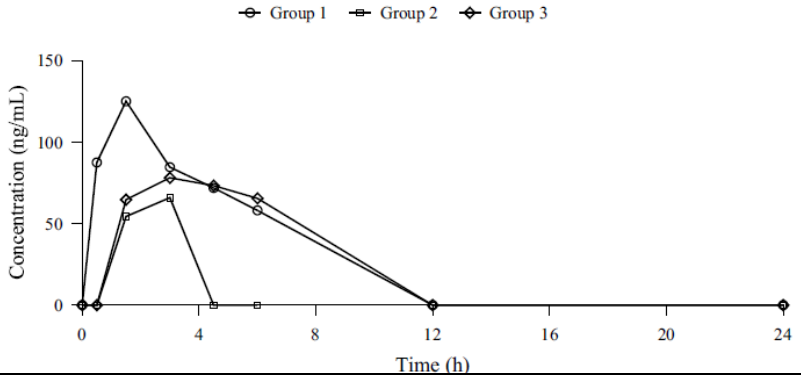


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Figure 19: Individual plasma OXC concentration-time profiles following a 4-week repeated once-daily oral administration of 15 mg/kg/day BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)

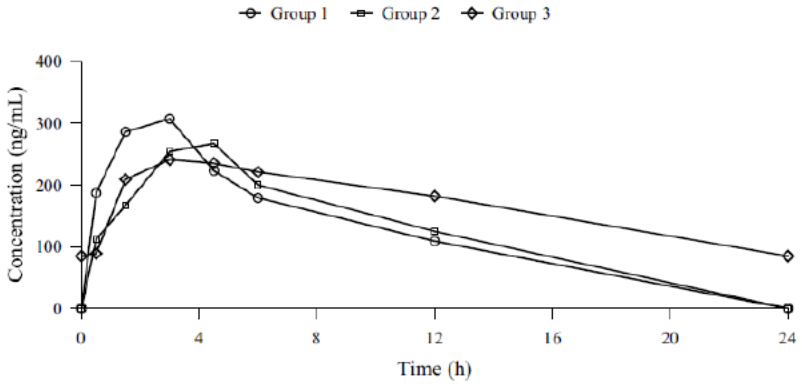
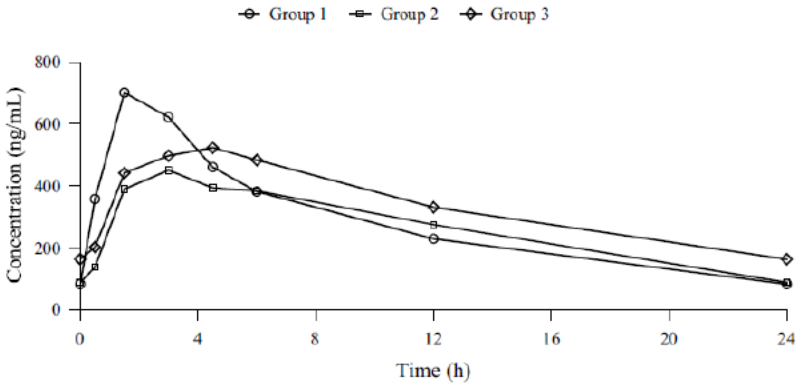


Figure 20: Individual plasma OXC concentration-time profiles following a 4-week repeated once-daily oral administration of 30 mg/kg/day of BIA 2-093 (Group 1: 2-6 yrs; Group 2: 7-11 yrs; Group 3: 12-17 yrs)



Efficacy Results	Seizure frequency for each patient was standardized to a frequency per 28 days period (i.e., mean daily frequency multiplied by 28). Changes in seizure frequency were analyzed for each age group separately. Especially in Group 1 (2-6 yrs) and Group 2 (7-11 yrs), the reported number of seizures at the baseline period was highly variable between patients (ranging from 5 to 4,665 seizures/28 days in Group 1 and from 7 to 1,183 seizures/28 days in Group 2). In Group 3, the number of seizures per 28 days ranged from 5 to 164. This large variability in the reported number of seizures largely decreased the accuracy and reliability of the efficacy assessments, especially because a very small number of patients were assessed in each age group (possibility of large data dispersion and incidental mean data variation). A dose-dependent decrease in relative (%) seizure frequency was observed in Group 1 (2-6 yrs) and Group 3 (12-17 yrs). Three patients became seizure-free during treatment with BIA 2-093, one patient in each age group: - Patient #115 [Group 1 (2-6 yrs)] became seizure-free on 15

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	mg/kg/day: seizure frequency was 174 seizures/28 days at baseline phase, 125 seizures/28 days during the 5 mg/kg/day phase, 0 seizures/28 days during the 15 mg/kg/day phase, and 5 seizures/28 days during the 30 mg/kg/day phase - Patient #208 [Group 2 (7-11 yrs)] reported 7 seizures/28 days during the baseline phase, and became seizure-free during the 5 mg/kg/day phase and remained seizure free for the further 2 dose levels. - Patient #308 [Group 3 (12-17 yrs)] reported 5 seizures/28 days during the baseline phase, and became seizure-free during the 5 mg/kg/day phase and remained seizure free for the further 2 dose levels. It should be emphasized that the present study was designed with pharmacokinetics as the primary endpoint. Due to the very small number of patients in each age group, the open-label nature of the study and the very large inter-patient variability in the reported number of seizures, the results must be interpreted with caution. Randomized, controlled, double-blind studies adequately powered for the efficacy endpoints are required.
Safety	No death. There were no severe AEs during the 5 mg/kg/day or 15 mg/kg/day treatment periods. There were a total of three severe AEs reported for the 31 randomized patients. Two severe AEs that occurred during the 30 mg/kg/day treatment period. There were 11 AEs reported during the 5mg/kg/day treatment period, 15 AEs during the 15 mg/kg/day treatment period, and 28 AEs during the 30 mg/kg/day treatment period. The most frequent reported AEs were upper respiratory tract infection and somnolence.
Conclusion	Similarly to what occurs in adult subjects, Eslicarbazepine acetate was rapidly metabolized to BIA 2-194 (S-licarbazepine), the major metabolite. Plasma levels of the parent drug usually remained below the limit of quantification, and BIA 2-195 (R-licarbazepine) and Oxcarbazepine were minor metabolites. BIA 2-194 showed dose-proportional pharmacokinetics in epileptic children of different age groups treated with Eslicarbazepine acetate concomitantly with anti-epileptic drugs.

In Vitro Study

Study **BI PHC#1 (SR-BI070104)**	Apparent permeability of BIA 2-093 in Caco-2 Cells.
Test System	Caco-2 cells
Study Center	No information.
Study Period	6/1/05 – 6/1/05
Study Objective	To evaluate the apparent permeability (Papp) of BIA 2-093 in Caco-2 cells.
Material and	Caco-2 cells were cultured in 12 well polycarbonate filter plates. Cell

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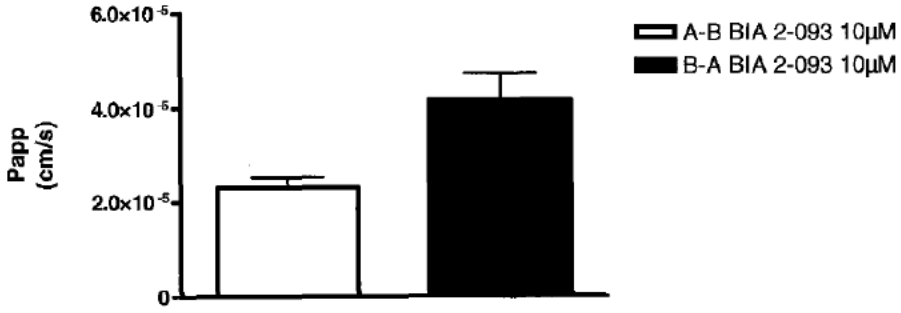
Methods	medium was aspirated and cells washed with Hanks at (pH 7.4, 4°C) 500 µl apical side and 1000 µl basal side. For apical-basal studies, Hanks (pH 7.4, 37°C) was added at 360 µl and 1000 µl to upper and lower chambers, respectively. For basal-apical studies Hanks (pH 7.4, 37°C) was added at 400 µl and 900 µl to the upper and lower chambers, respectively. Cells were pre-incubated (10 minutes, 37°C) with agitation and were then incubated for 3, 6, 12, and 30 minutes in the presence of 40 µl of a 10X solution of BIA 2-093 in apical side for apical-basal studies, or with 100 µl of a 10X solution of BIA 2-093 compound in basal side for basal-apical studies. Samples were analyzed by direct injection onto and HPLC-UV chromatography system and quantified by interpolation with a standard curve.
Results	BIA 2-093 (10 µM) shows an apparent permeability (Papp) of 2.3 x 10-5 and 4.2 x 10-5 for apical-basal and basal-apical respectively (Fig 1). This Papp indicates that BIA 2093 is a high permeable compound (Papp > lxl0-5 cm/s). Fig. 1 - Papp of BIA 2-093 at 37°C in Caco-2 cells  *Reviewer's comments: this is a very preliminary study. A positive control should be examined in the experiment.*

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Appendix 2: PHARMCOMETRIC REVIEW

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Reference ID: 3374277

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	022416
Drug Name	Eslicarbazepine Acetate
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	Sunovion Pharmaceuticals Inc.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following three key questions:

1.1.1 What dose of eslicarbazepine acetate, given once daily, is appropriate as an adjunctive therapy in the treatment of partial-onset seizures in adults?

Eslicarbazepine acetate (ESL) 800-1200 mg once daily oral dose (QD) is efficacious as an adjunctive therapy in the treatment of partial-onset seizures in adult patients based on pooled data of three Phase III studies BIA-2093-301, BIA-2093-302 and BIA-2093-304 (abbreviated as Study 301, 302 and 304 in this report, respectively). The efficacy of ESL 400 mg QD is not established in the Phase III studies.

- Primary efficacy (standard seizure frequency change from baseline) increased with ESL exposure across 400-1200 mg QD range (refer to the top two panels of Figure 1).
- Primary efficacy of ESL 800 mg and 1200 mg QD differentiated from placebo while efficacy of 400 mg QD was similar to placebo (refer to the top two panels of Figure 1).
- Secondary efficacy (responder rate of the patients) increased with ESL exposure across 400-1200 mg QD range (bottom two panels of Figure 1). A responder is a patient with seizure frequency reduced at least 50% from baseline due to the treatment.
- Secondary efficacy of ESL 800 mg and 1200 mg QD differentiated from placebo while efficacy of 400 mg QD was similar to placebo (bottom two panels of Figure 1).
- Higher ESL exposure resulted in higher adverse event rates in general; the safety profiles of ESL 800 and 1200 mg QD were acceptable in general (Figure 1).

In summary, ESL 800-1200 mg QD is efficacious as an adjunctive therapy in the treatment of partial-onset seizures in adult patients.

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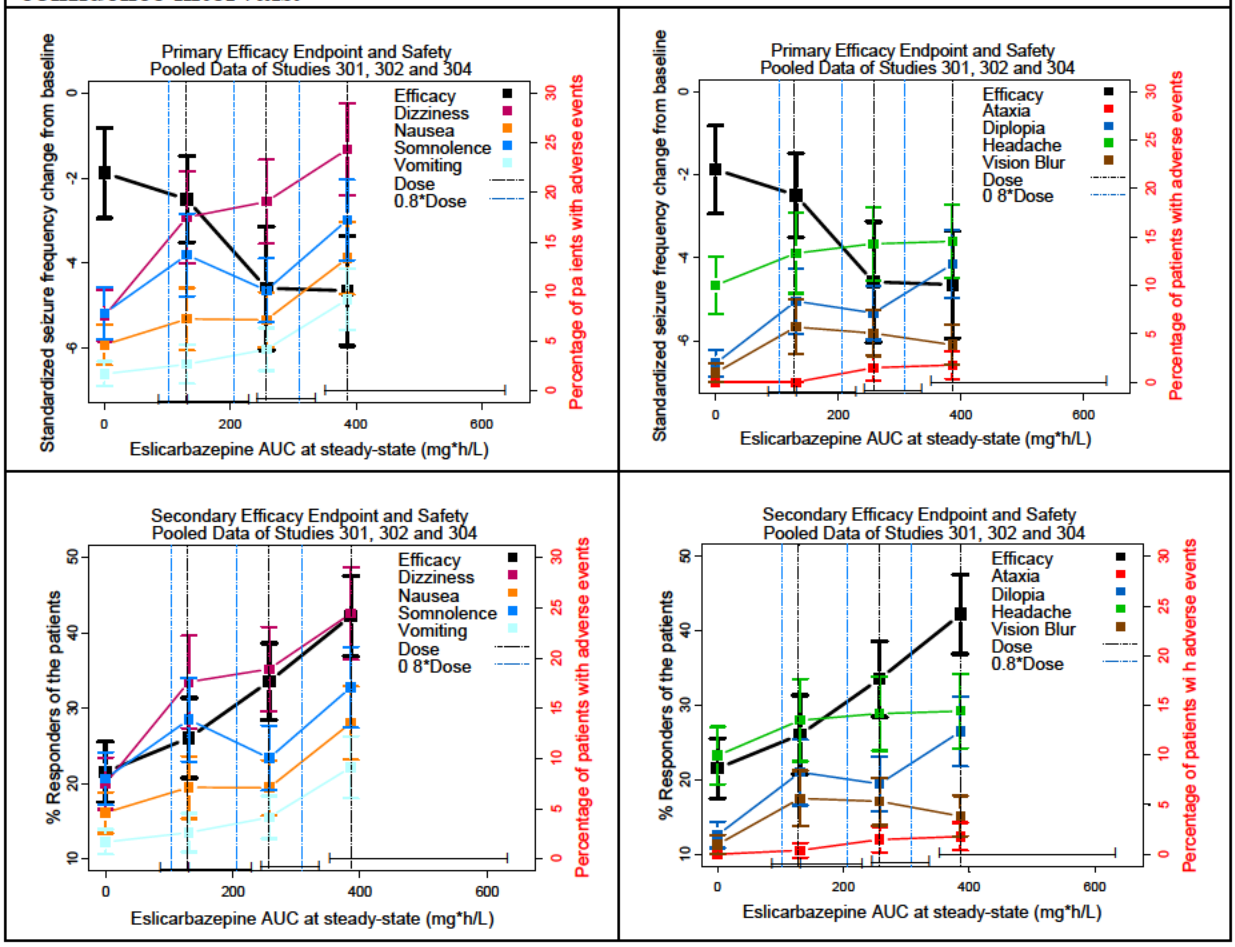
Figure 2. Change from baseline seizure frequency and percentage of patients with adverse events versus exposure profiles of pooled data of Phase III Studies BIA-2093-301, BIA-2093-302 and BIA-2093-304. Shown are the mean values and the 95% confidence intervals.



1.1.1 Is there any significant covariate that influences ESL PK and warrants ESL dose adjustment based on population PK analysis?

Yes, two conditions need dose adjustment based on sponsor's population PK analysis:

- The ESL dose should be increased by 50% when the patient co-administers ESL with phenobarbital or phenobarbital-like metabolic inducers (phenytoin and primidone). Co-administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin and primidone) reduced steady-state ESL exposure (AUC_{ss}) by 33.8% (refer to sponsor's population PK Report No. COG002419-2012-ESLIPK Page 9).
- The ESL dose should be increased by 50% when the patient co-administers ESL with carbamazepine. Co-administration of carbamazepine reduced ESL AUC_{ss} by 25.1-46.8% (refer to sponsor's population PK Report No. COG002419-2012-ESLIPK Page 9).

In summary, ESL dose should be increased by 50% when the patient co-administers ESL with carbamazepine; ESL dose should be increased by 50% when the patient co-administers ESL with phenobarbital or phenobarbital-like metabolic inducers (phenytoin and primidone). The sponsor did not identify any other covariates that warrant a dose adjustment based on the population PK analysis of ESL data from 11 Phase I studies and 3 Phase III studies.

1.1.2 Does ESL influence any anti-epilepsy drug's (AED's) PK that warrants the AED's dose adjustment based on population PK analysis?

No. Sponsor's population PK analysis suggests that no dose adjustment is needed for carbamazepine, valproate, levetiracetam, phenobarbital, phenytoin, or gabapentin when coadministered with ESL. There is no information on other AEDs in the population PK report.

Based on pooled data of Studies 301, 302 and 304, the sponsor developed population PK models for the 6 AEDs (carbamazepine, valproate, levetiracetam, phenobarbital, phenytoin, and gabapentin) and studied exposure interaction between ESL and each AED separately. ESL does not affect any of the 6 AED's exposure that warrants a dose adjustment based on the analysis results (refer to sponsor's population PK Report COG002419-2012-AEDPK Page 9-10).

1.2 Recommendations

The Pharmacometrics Division has reviewed NDA 022416 and the following is recommendation in labeling language.

1.3 Labeling Statement

----------DOSAGE AND ADMINISTRATION----------

- Coadministration with phenytoin and primidone: Dose of TRADENAME should be increased by 50% when coadministered with phenytoin or primidone.(7.2).
- Coadministration with carbamazepine: Dose of TRADENAME should be increased by 50% when coadministered with carbamazepine (7.2).

…….

12.3 Pharmacokinetics

The pharmacokinetics of eslicarbazepine are linear and dose-proportional in the dose range of 200 mg to 1200 mg once daily, both in healthy subjects and patients…

…….

Special Populations

……..

Race

No clinically significant effect of race (Caucasian N=849, Black N=~~24~~53, Asian N=65, and Other N=51) on the pharmacokinetics of eslicarbazepine was noted in a population pharmacokinetic analysis of pooled data from the (b) (4) clinical trials.

8 DRUG INTERACTIONS

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7.4 General Information

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7.5 Antiepileptics

The potential interactions between TRADENAME and AEDs are summarized in Table 5:

Table 5: Potential Interactions between TRADENAME and Concomitant Antiepileptic Drugs

AED Coadministered	AED Dose (mg/day) evaluated	TRADENAMEDose (mg/day) evaluated	Influence of TRADENAME on AED	Influence of AED on TRADENAME	Dosage Adjustment
Carbamazepine[a, b]	200-4200	1200	4-10% decrease in exposure	25-47% decrease in exposure	May need lower dose of carbamazepine based on tolerability [see *Adverse Reactions* (6)] May Need 50% higher dose of TRADENAME based on need for additional seizure control
Phenobarbital[a, c]	25-600	1200	No influence	34% decrease in exposure	Need 50% higher dose of TRADENAME
Phenytoin	100-700[a] 300[b]	1200 1200	No influence in epilepsy patients 35% increase in exposure in healthy volunteers	33% decrease in exposure in healthy volunteers	Monitor plasma phenytoin concentration; in epilepsy, dose adjustment may not be necessary & Need 50% higher dose of TRADENAME
Valproate[a]	200-5500	1200	No influence	No influence	None
Lamotrigine[b]	150	1200	14% decrease in exposure	4% decrease in exposure	None
Topiramate[b]	200	1200	18% decrease in exposure	7% decrease in exposure	None
Levetiracetam[a]	250-6000	1200	No influence	No influence	None
Gabapentin[a]	300-3600	1200	No influence	No influence	None

[a] Indicates the results in epilepsy patients.

[b] Indicates the results in healthy volunteers.

[c] Includes other AED enzyme inducers.

2 PERTINENT REGULATORY BACKGROUND

BIAL – Portela & C[a] S.A. (Bial), the original innovator of ESL, held a Pre-NDA meeting with the FDA on 23 January 2008. Afterwards, BIAL completed a transfer of ownership of the IND to Sunovion (formerly known as Sepracor) effective 10 April 2008 and Sunovion initiated NDA preparation activities. A Type C Meeting was held on 13 November 2008 between Sunovion and FDA, and the original NDA was submitted on 29 March 2009. Following a 13-month review,

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FDA issued a Complete Response (CR) letter on 30 April 2010. The CR letter identified concerns regarding audit findings and the design of the diary cards utilized in Studies 2093-301 and 2093-302, as well as discrepancies in clinical data noted in the NDA. The CR letter also requested additional data to address abuse liability concerns, nonclinical evaluation of genotoxicity, development of a 200 mg tablet, provided comments regarding the labeling and requested a complete safety update including any new studies.

Sunovion and BIAL twice met face to face with the FDA on 30 July 2010 and 07 June 2011 to discuss the plan for resubmission of the NDA. Substantial written correspondence between Sunovion and FDA occurred from 2010 to 2012 to clarify details of the plan and to obtain comments on both nonclinical and clinical protocols prior to the conduct of studies for meeting the requirements of the CR letter.

Population PK Evaluation of Eslicarbazepine Acetate for Adjunctive Therapy in Refractory Partial Onset Seizures

In the CR letter, FDA expressed concerns with studies 2093-301 and 2093-302 regarding diary design, study conduct, abuse potential, some nonclinical issues, and data presentation. In response to the CR letter, the results of a new Phase III Study, 2903-304 (which included some sites in North America and included a revised diary card design), were provided.

3 SPONSOR'S POPULATION PK ANALYSIS

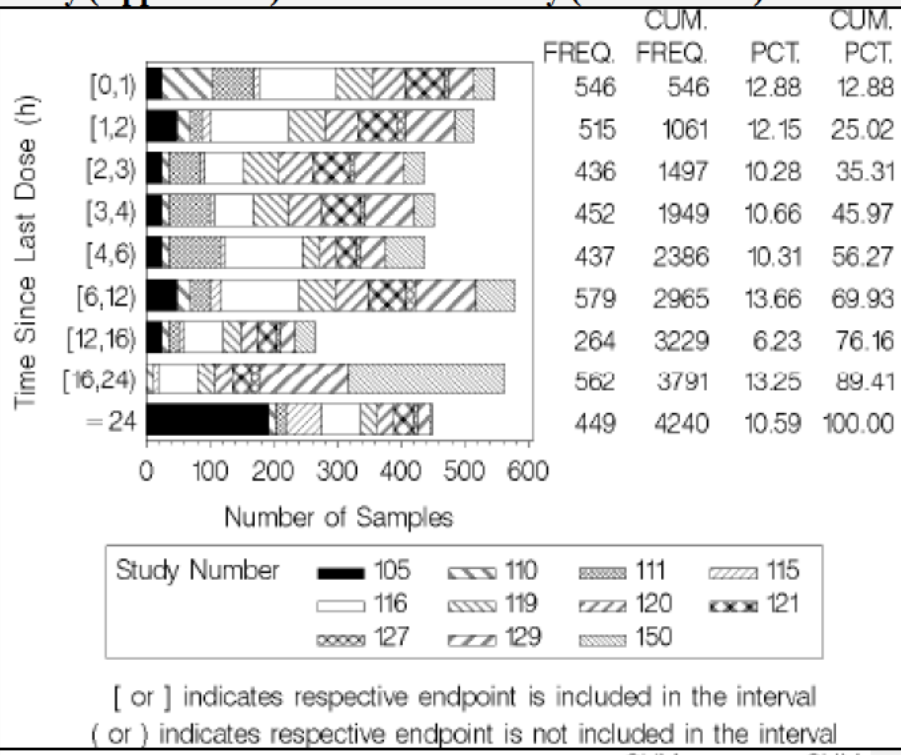
3.1 Population PK Evaluation of Eslicarbazepine Acetate for Adjunctive Therapy in Refractory Partial Onset Seizures

The objectives of the analyses were to:

- Develop a population pharmacokinetic (PK) model that describes the disposition of eslicarbazepine following oral administration of eslicarbazepine acetate in subjects enrolled in Phase 1 and Phase 3 studies, describing and quantifying the mean PK characteristics as well as the inter-individual variability (IIV) and residual variability (RV) in PK;
- Assess the influence of key demographic covariates and concomitant antiepileptic medications on the variability in population PK parameters; and
- Evaluate model performance in describing the data using a visual predictive check (VPC) technique.

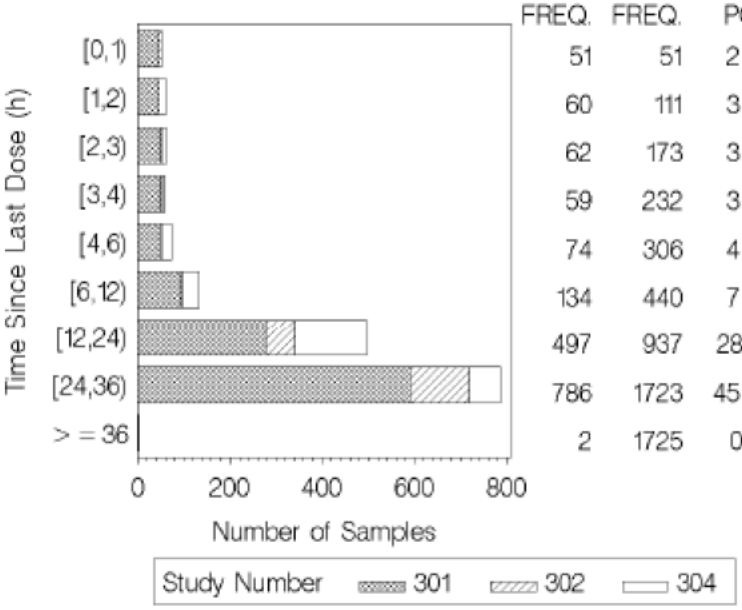
Data Description: Data for the population PK model development of eslicarbazepine were obtained from 11 densely sampled Phase 1 studies (BIA-2093-105, BIA-2093-110, BIA-2093-111, BIA-2093-115, BIA-2093-116, BIA-2093-119, BIA-2093-120, BIA-2093-121, BIA-2093-127, BIA-2093-129, and SEP093-150) and 3 sparsely sampled Phase 3 studies (SCO/BIA-2093-301, (b) (4) /BIA-2093-302, and BIA-2093-304). The Phase 1 data were limited to the Phase 3 clinical trial conditions which included only multiple 400-mg to 1200-mg doses administered once daily, with PK sampling within the 24-hour interval following dosing. The sample information is presented in **Figure 3**. Numbers of patients with AEDs administered are summarized in **Table 1**.

Figure 3. Frequency Distribution of Sample Time Since Last Dose Stratified by Phase I Study (Upper Panel) and Phase III Study (Lower Panel)



	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
[0,1)	546	546	12.88	12.88
[1,2)	515	1061	12.15	25.02
[2,3)	436	1497	10.28	35.31
[3,4)	452	1949	10.66	45.97
[4,6)	437	2386	10.31	56.27
[6,12)	579	2965	13.66	69.93
[12,16)	264	3229	6.23	76.16
[16,24)	562	3791	13.25	89.41
=24	449	4240	10.59	100.00

[or] indicates respective endpoint is included in the interval
(or) indicates respective endpoint is not included in the interval



	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
[0,1)	51	51	2.96	2.96
[1,2)	60	111	3.48	6.43
[2,3)	62	173	3.59	10.03
[3,4)	59	232	3.42	13.45
[4,6)	74	306	4.29	17.74
[6,12)	134	440	7.77	25.51
[12,24)	497	937	28.81	54.32
[24,36)	786	1723	45.57	99.88
>=36	2	1725	0.12	100.00

[or] indicates respective endpoint is included in the interval
(or) indicates respective endpoint is not included in the interval

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Table 1: Number of Subjects with AEDs administered

Concomitant Medications		Phase 1	Phase 3	Overall
Carbamazepine Flag, n (%)	No	206 (92.0)	411 (50.4)	617 (59.4)
	Yes	18 (8.0)	404 (49.6)	422 (40.6)
Clobazam Flag, n (%)	No	224 (100.0)	698 (85.6)	922 (88.7)
	Yes	0 (0.0)	117 (14.4)	117 (11.3)
Clonazepam Flag, n (%)	No	224 (100.0)	764 (93.7)	988 (95.1)
	Yes	0 (0.0)	51 (6.3)	51 (4.9)
Gabapentin Flag, n (%)	No	224 (100.0)	792 (97.2)	1016 (97.8)
	Yes	0 (0.0)	23 (2.8)	23 (2.2)
Lamotrigine Flag, n (%)	No	210 (93.8)	613 (75.2)	823 (79.2)
	Yes	14 (6.3)	202 (24.8)	216 (20.8)
Levetiracetam Flag, n (%)	No	224 (100.0)	670 (82.2)	894 (86.0)
	Yes	0 (0.0)	145 (17.8)	145 (14.0)
Phenobarbital Flag, n (%)	No	224 (100.0)	742 (91.0)	966 (93.0)
	Yes	0 (0.0)	73 (9.0)	73 (7.0)
Phenobarbital-Like Flag, n (%)[a]	No	209 (93.3)	676 (82.9)	885 (85.2)
	Yes	15 (6.7)	139 (17.1)	154 (14.8)
Phenytoin Flag, n (%)	No	209 (93.3)	744 (91.3)	953 (91.7)
	Yes	15 (6.7)	71 (8.7)	86 (8.3)
Pregabalin Flag, n (%)	No	224 (100.0)	805 (98.8)	1029 (99.0)
	Yes	0 (0.0)	10 (1.2)	10 (1.0)
Primidone Flag, n (%)	No	224 (100.0)	809 (99.3)	1033 (99.4)
	Yes	0 (0.0)	6 (0.7)	6 (0.6)
Tiagabine Flag, n (%)	No	224 (100.0)	807 (99.0)	1031 (99.2)
	Yes	0 (0.0)	8 (1.0)	8 (0.8)
Topiramate Flag, n (%)	No	211 (94.2)	710 (87.1)	921 (88.6)
	Yes	13 (5.8)	105 (12.9)	118 (11.4)
Valproate Flag, n (%)	No	224 (100.0)	626 (76.8)	850 (81.8)
	Yes	0 (0.0)	189 (23.2)	189 (18.2)
Vigabatrin Flag, n (%)	No	224 (100.0)	812 (99.6)	1036 (99.7)
	Yes	0 (0.0)	3 (0.4)	3 (0.3)
Zonisamide Flag, n (%)	No	224 (100.0)	798 (97.9)	1022 (98.4)
	Yes	0 (0.0)	17 (2.1)	17 (1.6)

[a] phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone).

Dose Administration: Eslicarbazepine acetate was administered orally in tablet formulation. In the Phase 1 studies, multiple eslicarbazepine acetate doses administered once daily of 400, 600, 800, 900, or 1200 mg were studied. The eslicarbazepine acetate doses for the Phase 3 studies were 400, 800, or 1200 mg once daily.

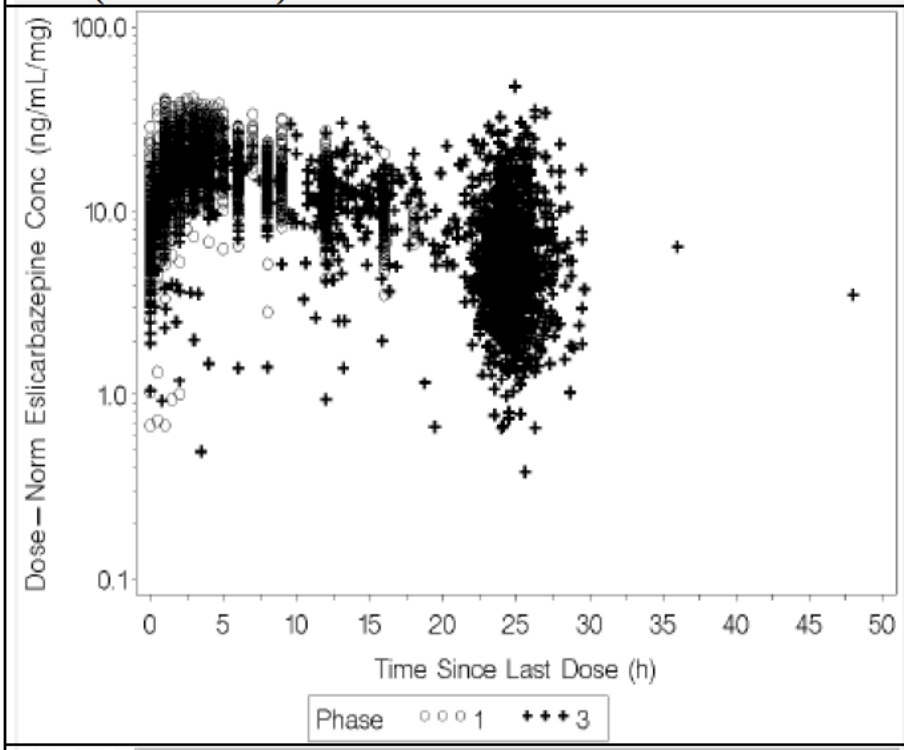
Pharmacokinetic Sample Collection: Plasma samples for determination of eslicarbazepine concentrations were collected at frequent intervals from 0.5 to 24 hours post-dose for all the Phase 1 studies and Part III of Study SCO/BIA-2093-301. Each individual contributed between 8 and 28 plasma samples.
Sparse samples were collected in Part I and Part II of Studies SCO/BIA-2093-301 and [redacted] BIA-2093-302, and Part I of Study BIA-2093-304. Although subjects in these studies contributed between 1 and 4 plasma samples, a substantial number of subjects contributed only 1 or 2 plasma samples.

Population Pharmacokinetic Analysis Methodology: Key steps of the population PK analysis were: exploratory data analysis, application of the previously developed population PK model, evaluation of covariate effects, model refinement, and model evaluation.
Based upon preliminary graphical examination of eslicarbazepine concentration–time data, the previously developed population PK structural model without covariate effects (except body weight) for eslicarbazepine (based on three Phase 3 studies) was initially applied to data from eleven Phase 1 studies and three Phase 3 studies and further refined. An exponential model was used to describe the IIV in absorption rate constant (ka), apparent oral clearance (CL/F), and apparent volume of distribution (V/F). Two log error models were used to describe the residual error for Phase 1 and Phase 3 studies, respectively.
Following the development of an appropriate structural PK model, the influence of subject covariates on selected PK parameters for eslicarbazepine was evaluated. The demographic and clinical covariates that were assessed included gender, race, age, weight, height, body mass index (BMI), and creatinine clearance (CrCL). The following concomitant antiepileptic drugs (AEDs) were evaluated: carbamazepine, valproic acid, lamotrigine, topiramate, levetiracetam, phenobarbital, clonazepam, primidone, phenytoin, pregabalin, gabapentin, vigabatrin, zonisamide, clobazam, and tiagabine. The effect of concomitant AEDs was analyzed sequentially, first by presence/absence, then, if significant, by the effect of doses and/or the effect of concentrations. A univariate analysis–backward elimination method was used in the covariate analysis to identify statistically significant predictors of PK variability.
The final model was validated using a simulation-based VPC methodology to assess concordance between the model-based simulated data and the observed data.

Population Pharmacokinetic Analysis Results: The final population PK model was a 1-compartment model with first-order absorption and first-order elimination, parameterized in terms of ka, CL/F, and V/F, with IIV estimated for ka, CL/F, and V/F using exponential error models. Two separate additive plus proportional error models were employed to allow for differences in the magnitude of RV between Phase 1 and Phase 3 data. The parameter estimates were associated with good precision. The magnitude of the inter-individual variability was large for ka, but was moderate for CL/F and V/F. Residual variability for the Phase 3 data was moderate. Residual variability for the Phase 1 data was relatively small. Creatinine clearance, body weight, dose of concomitant carbamazepine, and concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) were statistically significant predictors of CL/F. Body weight, gender, and concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) were statistically significant predictors of V/F.

Reference ID: 3374277

Figure 4. Dose Normalized Plasma Eslicarbazepine Concentrations Since Last Dose Stratified by Study Phase (Upper Panel) and by Dose (Lower Panel)



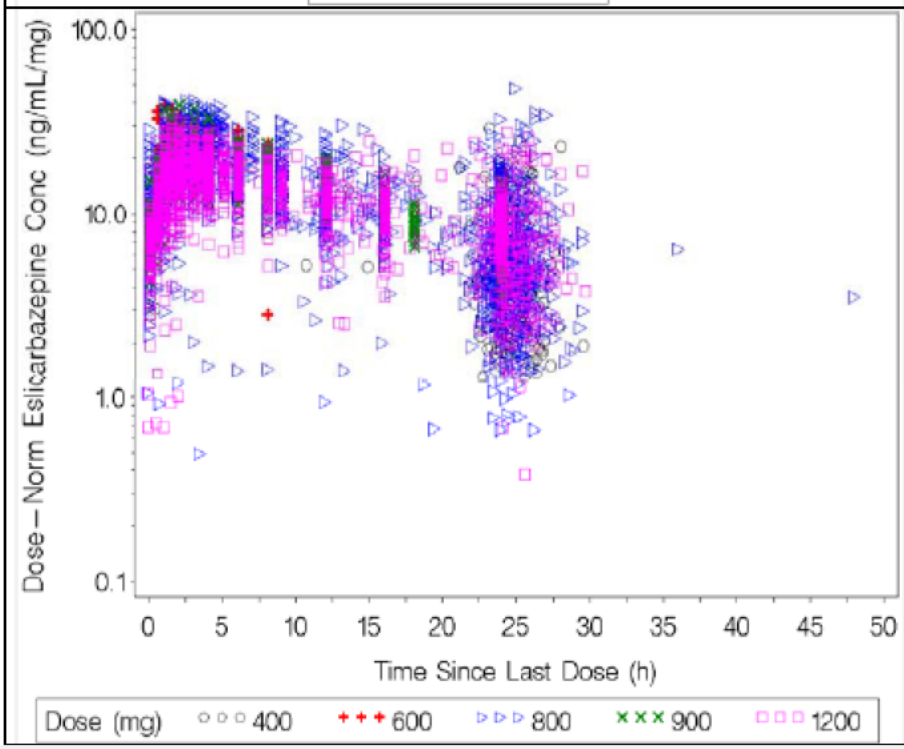
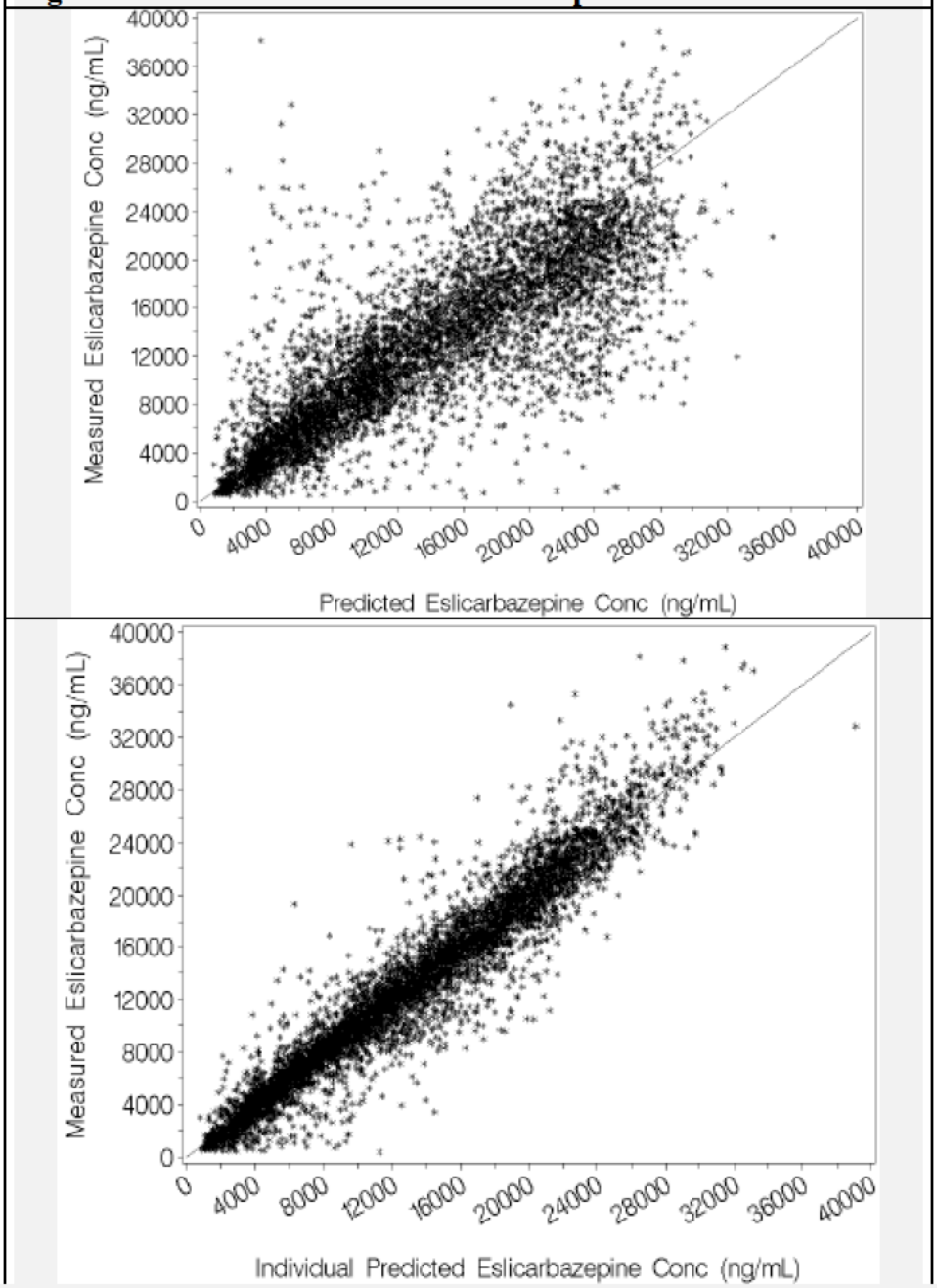


Figure 5. Goodness of Fit for the Final Population PK Model



The population mean parameter estimates and their associated precisions (%SEM) for the final PK model of eslicarbazepine are presented in the table below.

Table 2: The results of the final population PK model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
k_a (h^{-1})	2.34	9.6	126.49	18.4
CL/F for No Carbamazepine Use (L/h)	2.43	1.3	27.04	10.5
Additive Shift of Concomitant Phenobarbital or Phenobarbital-Like Inducers (Phenytoin, Primidone) on CL/F (L/h)	1.24	6.7		
Slope Term for Effect of Body Weight on CL/F (L/h/kg)	0.0132	24.0		
Power Term for Effect of Creatinine Clearance on CL/F	0.195	33.9		
Additional CL/F When Carbamazepine Dose = 800 mg (L/h)	1.08	5.4		
Power Term for Effect of Carbamazepine Dose on CL/F	0.411	35.8		
V/F (L)	61.3	2.0	17.69	15.6
Additive Shift of Female Gender on V/F (L)	-9.9	18.2		
Additive Shift of Concomitant Phenobarbital or Phenobarbital-Like Inducers (Phenytoin, Primidone) on V/F (L)	12.0	30.3		
Power Term for Effect of Body Weight on V/F	0.617	15.0		
Ratio of Additive/Proportional RV Components[c] (σ_2/σ_1), Phase 1	4520	18.4	NA[d]	NA
Proportional RV Component (σ_1), Phase 1	0.0124	7.8	NA	NA
Ratio of Additive/Proportional RV Components[e] (σ_1/σ_2), Phase 3	0.0000632	31.6	NA	NA
Additive RV Component (σ_2), Phase 3	5290000	17.1	NA	NA
Minimum value of the objective function = 99315.706				

[a] %CV = percent coefficient of variation.
[b] %SEM = percent standard error of the mean.
[c] Residual variability was estimated to range from 23.74 %CV to 11.24 %CV at predicted eslicarbazepine concentrations ranging from 2400 ng/mL to 33000 ng/mL, respectively.
[d] NA = not applicable.
[e] Residual variability was estimated to range from 311.15 %CV to 15.68 %CV at predicted eslicarbazepine concentrations ranging from 740 ng/mL to 39200 ng/mL, respectively.

Population Pharmacokinetic Conclusions:

- The PK of eslicarbazepine is described by a 1-compartment model with first-order absorption and linear elimination. The estimated base eslicarbazepine CL/F, V/F, and first-order absorption half-life (t1/2) are 2.43 L/h, 61.3 L, and 0.296 h, respectively.
- The concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) resulted in lower (33.8%) eslicarbazepine area under the concentration-time curve at steady-state (AUCss) compared to subjects administered no other AEDs. A higher dose of eslicarbazepine acetate may be necessary to achieve the same eslicarbazepine exposure with concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone).
- Subjects administered carbamazepine had a lower eslicarbazepine AUCss [range: 25.1% - 34.4% (median reduction of 30.8% with co-administration of carbamazepine 400 mg

twice daily) for carbamazepine doses ranging from 200 mg twice daily to 400 mg three times daily] compared to subjects administered no other AEDs. Dose adjustment of eslicarbazepine is not warranted due to the increased potential for adverse events.

- The concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) resulted in higher (19.6%) eslicarbazepine V/F compared to subjects administered no other AEDs. This increase in V/F is not expected to be clinically relevant.
- Apparent oral clearance of eslicarbazepine increases with increasing CrCL according to a power function. A hypothetical subject with an estimated CrCL of 80 or 50 mL/min, and a body weight of 70 kg will have a higher (7.5% and 17.8%, respectively) eslicarbazepine AUCss as compared to a hypothetical subject with the median CrCL of 115.7 mL/min and a body weight of 70 kg, assuming no concomitant AEDs were administered.
- Eslicarbazepine CL/F increases in proportion to body weight. For a hypothetical subject with a body weight of 34 or 140 kg, a CrCL of 115.7 mL/min, and not receiving concomitant AEDs, eslicarbazepine AUCss would be 24.3% higher and 27.5% lower, respectively, relative to a hypothetical subject with a body weight of 70 kg, a CrCL of 115.7 mL/min, and not receiving concomitant AEDs. Thus, for most adult subjects, eslicarbazepine acetate dose may not require adjustment based on weight.
- Apparent volume of distribution increases with increasing body weight according to a power function. In a hypothetical female subject with a body weight of 62, 70, or 81 kg, eslicarbazepine V/F is predicted to be 47.7, 51.4, and 56.2 L. The distribution volume for a male subject at the same body weights would be 56.9, 61.3, and 67.1 L. These differences are not expected to be clinically relevant.
- Female subjects had a lower (16.15%) eslicarbazepine V/F compared to male subjects. This small gender difference in V/F is not expected to be clinically relevant.

Table 3: Influence of Concomitant Antiepileptic Drugs on Eslicarbazepine PK

AED Coadministered	AED Dose (mg/day) Evaluated	Eslicarbazepine Acetate Dose (mg/day) Evaluated	Influence of AED on Eslicarbazepine Acetate*	Dosage Adjustment
Carbamazepine	200-4,200	400-1,200	25.1%-46.8% decrease in exposure	dose adjustment of eslicarbazepine acetate is not warranted due to the increased potential for adverse events
Phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone)	50-600 (phenobarbital) 100-2,000 (phenytoin) 300-1,000 (primidone)	400-1,200	33.8% decrease in exposure	may need higher dose of eslicarbazepine acetate
Valproate	300-4,000	400-1,200	no influence	none
Lamotrigine	25-1,400	400-1,200	no influence	none
Levetiracetam	250-6,000	400-1,200	no influence	none

* Exposure based on AUC

3.2 Population PK Analysis of Antiepileptic Drugs after Administration of Eslicarbazepine Acetate in Patients with Epilepsy

The objectives of the analyses were to refine the previously developed population PK models for 6 antiepileptic drugs (AEDs) using data from 3 Phase III studies, and perform covariate analyses to characterize the effect of eslicarbazepine acetate on the PK of the 6 AEDs after accounting for the effects of other potential factors that may influence PK variability. Population PK models were not developed for lamotrigine and topiramate as previous Phase I studies have shown no clinically relevant effect of eslicarbazepine on the PK of these drugs.

Data Description: Data from 3 Phase III studies were used for this pooled data analysis. Studies 2093-301, 2093-302, and 2093-304 were multi-part, multicenter studies designed to evaluate the efficacy of eslicarbazepine acetate administered once daily at doses of 400 mg (2093-301 and 2093-302 only), 800 mg, and 1,200 mg compared to placebo as adjunctive therapy in patients with refractory partial epilepsy. Sparse concentration data from Parts I and II in Study 2093-301 (**Table 4**) and Part I in Studies 2093-302 and 2093-304 (**Table 5**) were used for these analyses.

Table 4: Sampling schedule of Study 2093-301 for population PK analysis Concomitant Antiepileptic Drugs and Eslicarbazepine

		Double-Blind (Part I)					1-Year Open-Label Extension (Part II)					
Visit	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Disc
Weeks/months	-8 Weeks	Day 1	2 Weeks	4 Weeks	8 Weeks	14 Weeks	+ 1 Month	+ 3 Months	+ 6 Months	+ 9 Months	+ 12 Months	
Blood sampling for AED concentrations		X				X	X		X		X	X

Table 5: Sampling schedule of Studies 2093-302 and 2093-304 for population PK analysis Concomitant Antiepileptic Drugs and Eslicarbazepine

		Double-Blind (Part I)						1-Year Open-Label Extension (Part II)					
Visit	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Disc
Weeks/months	-8 Weeks	Day 1	2 Weeks	4 Weeks	8 Weeks	14 Weeks	18 Weeks	+ 1 Month	+ 3 Months	+ 6 Months	+ 9 Months	+ 12 Months	
Blood sampling for AED concentrations		X				X	X	X		X		X	X

Abbreviations: AED, antiepileptic drug; Disc, upon early termination; TC, telephone contact during the 12-week maintenance period.

Treatment Regimen: In Part I of each study, an 8-week baseline period (single-blind placebo in Study 2093-301) was followed by a double-blind 2-week titration period, a 12-week maintenance period, and a tapering-off period of 4 weeks in Study 2093-301 and 2 weeks in Study 2093-304 for patients not continuing to Part II. In each study, Part II was a 1-year open-label extension with a starting dose of 800 mg for 1 month, after which doses could be titrated up or down. Following the baseline period, patients were randomized to once-daily eslicarbazepine acetate at 400 mg (Studies 2093-301 and 2093-302), 800 mg, or 1,200 mg or placebo.

Pharmacokinetic Sample Collection: Blood samples collected from patients in the 3 studies were intended to be exclusively sparse samples, drawn before dosing on selected visits. Only data from Parts I and II (Study 2093-301 only) were used for this analysis.

Population Descriptions: The AED populations consisted of exclusively adult patients with evaluable PK data (with fully documented AED dosing and sampling information). Depending on the eslicarbazepine acetate study, the resulting populations treated with the selected AED were as follows: Carbamazepine: 628 patients (212 patients from 2093-301, 200 patients from 2093-302, and 216 patients from 2093-304)

Valproate: 262 patients (88 patients from 2093-301, 70 patients from 2093-302, and 104 patients from 2093-304)

Levetiracetam: 232 patients (33 patients from 2093-301 and 57 patients from 2093-302, and 142 patients from 2093-304)

Phenobarbital: 115 patients (31 patients from 2093-301, 47 patients from 2093-302, and 37 patients from 2093-304)

Phenytoin: 106 patients (7 patients from 2093-301, 45 patients from 2093-302, and 54 patients from 2093-304)

Gabapentin: 29 patients (18 patients from 2093-301, 6 patients from 2093-302, and 5 patients from 2093-304)

Patients with at least 3 (Study 2093-304 only) or 4 partial-onset seizures per 4 weeks during the baseline period, with a total of 8 seizures in the 8-week baseline period, aged 18 years or more (Study 2093-304: 16 years or more), and currently receiving treatment with 1 or 2 (Study 2093-302 allowed up to 3) AEDs in a stable dose regimen were randomized to treatment.

Population PK Analysis Methods: Using NONMEM® Version VI, Level 2.0 (ICON-2006), structural model for the PK of each compound was developed initially, including error models. Selected covariates were then added as necessary, using a predefined strategy. Characteristics of acceptable models were defined and models were refined as necessary.

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For each AED, a simplified population model of apparent oral clearance (CL/F) was used to predict the average steady-state concentration (Cavss), which was compared to steady-state AED concentrations observed at each visit.

Based on the covariates identified to be significant in the previous AED model development analyses, the covariates evaluated for potential influence on variability in CL/F included: race (carbamazepine), weight (gabapentin),

creatinine clearance (CrCL) (gabapentin, levetiracetam), liver function tests, including: alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (carbamazepine, phenobarbital, phenytoin, and valproate), concurrent AEDs (carbamazepine, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, topiramate, and valproate) assessed sequentially by presence/absence, then by effect of dose, and/or concentration, and eslicarbazepine exposure (presence/absence, then dose, and/or concentration).

Application of PK Model: The previously developed population PK structural models without covariate effects for the 6 AEDs were applied and further refined based on drug concentration data from the 3 Phase III studies. These models estimate only the CL/F, which is sufficient to predict steady-state average concentrations (Cav-ss):

$$C_{av-ss} = \frac{R_0}{CL/F}$$

Where:

C_{av-ss}	=	AED steady-state average concentration
R_0	=	dosing rate (mg/h); that is, total daily dose divided by 24
CL/F	=	apparent oral clearance (L/h)

An exponential model was used to describe the IIV in CL/F. Additive RV models were applied for the PK models of carbamazepine, valproate, levetiracetam, and phenobarbital, an additive plus proportional RV model was applied for the PK model of gabapentin and a log error model was applied for phenytoin, as a starting point for the evaluation of RV models. Selection of the simplest base structural model was based on the smallest objective function and by inspection of the patterns in the residual plots.

Population PK Results: The population PK model for carbamazepine (628 patients, 1,451 concentrations) included only an effect of carbamazepine dose, total bilirubin, and eslicarbazepine acetate dose as statistically significant predictors of carbamazepine CL/F.

The population PK model for valproate (262 patients, 622 concentrations) included the effects of only valproate dose and carbamazepine dose as statistically significant predictors of valproate CL/F. No effect of eslicarbazepine acetate on the CL/F of valproate was detected.

The population PK model for levetiracetam (232 patients, 398 concentrations) included the statistically significant influence of CrCL, carbamazepine dose and levetiracetam dose on levetiracetam CL/F. No effect of eslicarbazepine acetate on the CL/F of levetiracetam was detected.

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Only the dose of phenobarbital was found to be a statistically significant predictor of phenobarbital CL/F. No effect of eslicarbazepine acetate on the CL/F of phenobarbital was detected.

No covariates were found to be statistically significant predictors of phenytoin CL/F.

For gabapentin (29 patients, 90 concentrations), the population PK model included only an effect of CrCL as a statistically significant finding. No effect of eslicarbazepine acetate on the CL/F of gabapentin was detected.

Clinical Relevance of Covariates:

Based on the covariate analysis of the effect of eslicarbazepine acetate on concurrent AEDs, the potential interactions between eslicarbazepine acetate and AEDs are summarized in the table below.

Table 6: Influence of Eslicarbazepine on Concomitant Antiepileptic Drugs

AED Coadministered	AED Dose (mg/day) Evaluated	Eslicarbazepine Acetate Dose (mg/day) Evaluated	Influence of Eslicarbazepine Acetate on AED	Dosage Adjustment
Carbamazepine	200-4200	400-1200	4%-10% decrease in exposure	none
Valproate	200-5500	400-1200	no influence	none
Levetiracetam	250-6000	400-1200	no influence	none
Phenobarbital	25-600	400-1200	no influence	none
Phenytoin	100-700	400-1200	no influence	none[a]
Gabapentin	300-3600	400-1200	no influence	none

[a] Monitor plasma phenytoin concentrations.

Population PK Conclusions:

- Population PK models were developed for 6 AEDs (carbamazepine, valproate, levetiracetam, phenobarbital, phenytoin, and gabapentin), estimating the CL/F of each drug and evaluating the effect of factors influencing variability in CL/F, including the effect of eslicarbazepine acetate exposure (presence, dose, or concentration).
- Population PK models were not developed for lamotrigine and topiramate as previous Phase I studies had shown no clinically relevant effect of eslicarbazepine acetate on the PK of these drugs.
- The effect of eslicarbazepine acetate on carbamazepine PK was minor. Carbamazepine CL/F was increased with increasing eslicarbazepine acetate dose, carbamazepine dose, and total bilirubin. For patients having the population median value of total bilirubin (0.29 mg/dL), carbamazepine CL/F is expected to increase 3.73%, 7.46%, and 11.27% with the combination of 1,000 mg carbamazepine daily and 400, 800, or 1,200 mg eslicarbazepine acetate daily, respectively, over the predicted CL/F without eslicarbazepine acetate. The corresponding reductions in carbamazepine exposure (Cavss) were 3.53%, 6.98%, and 10.03%, respectively. These reductions in carbamazepine exposure are not likely to be clinically relevant. Factors other than eslicarbazepine were as follows:

--Carbamazepine CL/F increased slightly with increasing total bilirubin; the effect was minor. Differences in carbamazepine CL/F over the observed range of total bilirubin values were not considered clinically relevant.

--Neither race nor other liver function tests (ALT, ALP, AST) were found to be significant predictors of carbamazepine CL/F.

- Eslicarbazepine acetate administration did not affect valproate PK parameters. Factors whichinfluenced valproate CL/F were:

--The doses of both carbamazepine and valproate were shown to be significant predictors of valproate CL/F, where increasing doses of either drug were associated with increased valproate CL/F. However, neither concomitant administration of lamotrigine nor liver function tests (AST, ALT, ALP, total bilirubin) were significant predictors of valproate CL/F.

- Eslicarbazepine acetate administration did not affect levetiracetam PK parameters. In patients receiving the median levetiracetam dose of 2,500 mg, the CL/F of levetiracetam was between 11.9% and 95.6% higher in patients with the population median value of CrCL (108.5 mL/min) who were coadministered carbamazepine at doses ranging from 300 mg to 2,400 mg as compared to those not receiving concomitant carbamazepine. Creatinine clearance was also found to be a statistically significant predictor of levetiracetam CL/F.

--Concomitant administration of lamotrigine was not found to be a significant predictor of levetiracetam CL/F.

- Eslicarbazepine acetate administration did not affect phenobarbital CL/F. The only significant predictor of phenobarbital CL/F was the administered dose of phenobarbital; concomitant administration of carbamazepine and liver function tests (AST, ALT, ALP, total bilirubin) were not significant predictors of phenobarbital CL/F.
- Eslicarbazepine acetate administration did not affect phenytoin PK parameters. Phenytoin dose and liver function tests (AST, ALT, ALP, total bilirubin) were not significant predictors of phenytoin CL/F. Note that the findings from the population PK evaluations were different from the findings of the dedicated Phase I DDI study of eslicarbazepine acetate and phenytoin (Study 2093-121), which found a decrease in eslicarbazepine exposure and an increase in phenytoin exposure for combined administration, compared to administration of either agent alone.
- Eslicarbazepine acetate administration did not affect gabapentin PK parameters. Gabapentin CL/F is related to CrCL in a proportional linear manner, however, body weight was not found to be a statistically significant predictor of gabapentin CL/F.
- Based on these population PK analyses, no influence of eslicarbazepine acetate on other AEDs was detected when eslicarbazepine acetate was coadministered with valproate, levetiracetam, phenobarbital, phenytoin, or gabapentin.

Reviewer's comments on Sponsor's Population PK Analyses: *A quantitative analysis assessing the covariate effects on ESL exposure was performed using population PK methodology. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data well. With regard to the covariates chosen, the reviewer's forward selection were based on only univariate analysis (refer to Table 15 in Page 80-81 of the sponsor's population sponsor's*

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*population PK Report No. COG002419-2012-ESLIPK), therefore, no multivariate analyses were executed for possible interaction effect(s) of covariates. The PK data from renal impairment study (*BIA-2093-112*) was not included in the population PK analysis, so the effect of creatinine on ESL dose adjustment is not investigated in this analysis.*

Another population analysis assessed the effects of ESL on the exposures of six AEDs. The model assumes that the sparse PK samples of each AED represented average steady-state concentration of the AED.

4 FDA REVIEWER'S ANALYSIS

4.1 Objective

The purpose of FDA reviewer's analysis was to evaluate what dose of eslicarbazepine acetate, given once daily, is appropriate as an adjunctive therapy in the treatment of partial-onset seizures in adults.

4.2 Methods and Software

For the objective, TIBCO Spotfire S-PLUS 8.0 was used for data organization, nonlinear modeling as well as graphical and statistical analysis based on sponsor's datasets.
In the nonlinear modeling analysis, the following equation was used:

$$E = E_0 + \frac{E_{\max} \times C_{avss}}{EC_{50} + C_{avss}} \qquad \text{Equation 1}$$

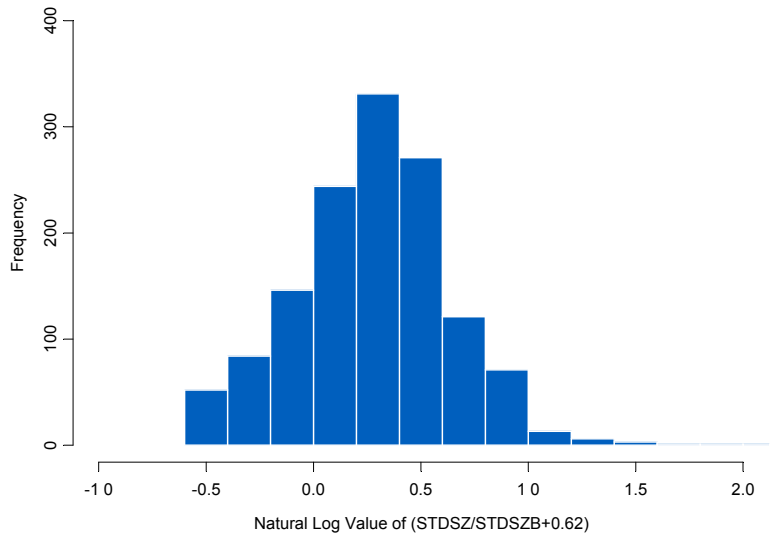
Where E_0 is placebo effect (to be estimated by the modeling), E_{max} is the maximum effect of ESL (to be estimated by the modeling), EC_{50} is steady-state ESL average concentration that produce 50% E_{max} effect (to be estimated by the modeling), C_{avss} is steady-state ESL average concentration (generated by the population PK analysis as observed independent variable). At a specific C_{avss} value of a specific patient, E is either 0 or 1 observed of the individual patient for the secondary efficacy endpoint (responder or non-responder), or E is the transformed value of observed primary efficacy results of the individual patient based on the following formula:

$$E = \log_e(\frac{Stdsz}{Stdszb} + 0.62) \qquad \text{Equation 2}$$

Where *Stdsz* is Standardized Seizure Frequency at steady-state of ESL maintenance dose and *Stdszb* is Standardized Seizure Frequency at baseline of the patient. The transformation is executed so that the frequency of observed *E* values of the whole patient population is normally distributed (as shown in **Figure 6**).

Figure 6: The distribution of transformed data for the primary efficacy endpoint

Reference ID: 3374277



STDSZ: standardized seizure frequency at eslicarbazepine maintenance phase; STDSZB: standardized seizure frequency at baseline

4.3 Datasets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Data Source	Dataset Names	Link to EDR
Data from Phase 3 studies	eff301.xpt eff302.xpt eff304.xpt ae01.xpt ae302.xpt ae304.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Eslicarbazepine_NDA022416_HL\Spnsor's data and analyses
Data from pop-PK analysis output	`final-model.tbl.txt`	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Eslicarbazepine_NDA022416_HL\Spnsor's data and analyses

4.4 Results

The fitting curve versus observed data for the primary efficacy endpoint is presented in **Figure 7**. The parameter estimates of the E_{max} model on the primary efficacy endpoint are listed in **Table 8**. A general linear model (with intercept and slope as parameters) between E and C_{avss} fitted the data and resulted in log likelihood value of -544.9, which was 2.8 lower than -542.1 for the E_{max} model.

Table 8. Parameter estimates of the E_{max} model on the primary efficacy endpoint

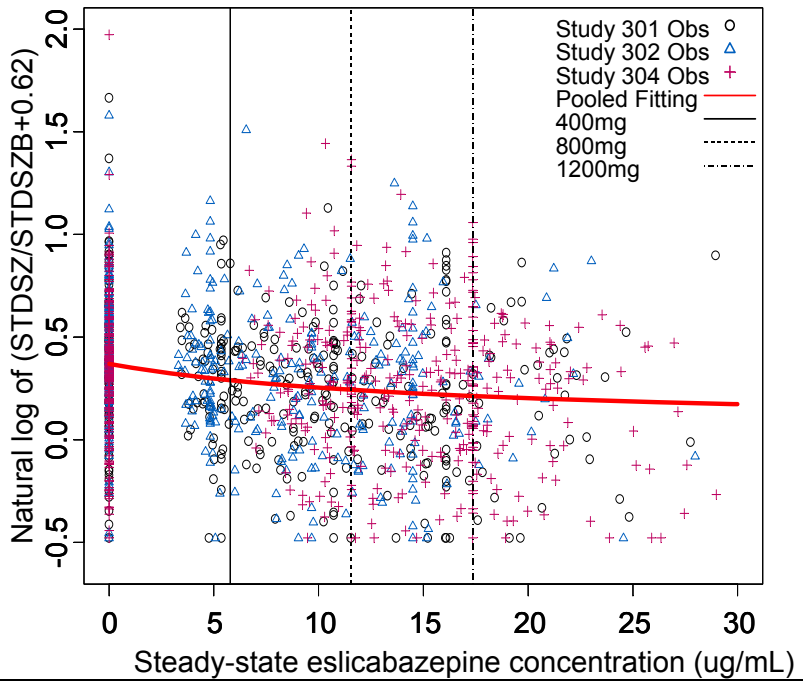
	E_0	E_{max}	EC_{50} (mcg/mL)
Mean	0.370	-0.300	15.7
SE	0.018	0.172	17.3

Reference ID: 3374277

According to Equation 2, the corresponding Stdsz/Stdszb (Standardized Seizure Frequency at Maintenance Phase divided by Standardized Seizure Frequency at Baseline) ratio population mean (90%CI_{low}, 90%CI_{high}) is 0.828 (0.778, 0.880) due to the placebo treatment, calculated based on E_0=0.370 and SE=0.018. When ESL is administered, the population mean ratio (90%CI_{low}, 90%CI_{high}) of Stdsz/Stdszb is 0.453 (0.146, 0.882). Corresponding to population EC_{50} (SE) of 15.7 (17.3) mcg/mL, the population mean ED_{50} (SE) is 121 (133) mg QD, and these high SE values indicated large inter-subject variability in the drug effect.

.

Figure 7: The fitting curve versus observed data for the primary efficacy endpoint



The fitting curve versus observed data for the secondary efficacy endpoint (responder rate) is presented in **Figure 8**, and the parameter estimates of the E_{max} model on the secondary efficacy endpoint are listed in **Table 9**. A general linear model (with intercept and slope as parameters) between E and C_{avss} fitted the data and resulted in log likelihood value of -849.2, which was 1.2 lower than -848.0 for the E_{max} model.

Table 9. Parameter estimates of the E_{max} model on the secondary efficacy endpoint

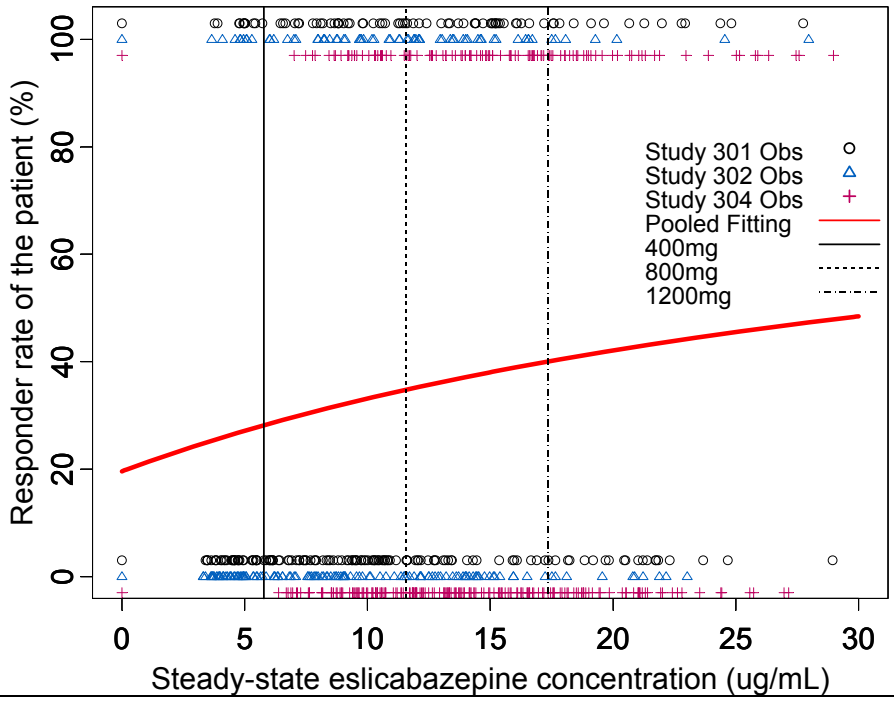
	E_0	E_{max}	EC_{50} (mcg/mL)
Mean	0.196	0.663	39.0
SE	0.022	0.637	53.2

The population mean (90%CI_{low}, 90%CI_{high}) responder rate is 0.196 (0.153, 0.239) due to the placebo treatment, calculated based on E_0=0.196 and SE=0.022. When ESL is administered, the $(Responder\%)_{max}$ (maximum mean responder rate of the population) is 0.859 assuming ESL dose has no cap. The SE of $(Responder\%)_{max}$ is as high as 0.637, and this high SE value indicated large inter-subject variability in the drug effect.

Reference ID: 3374277

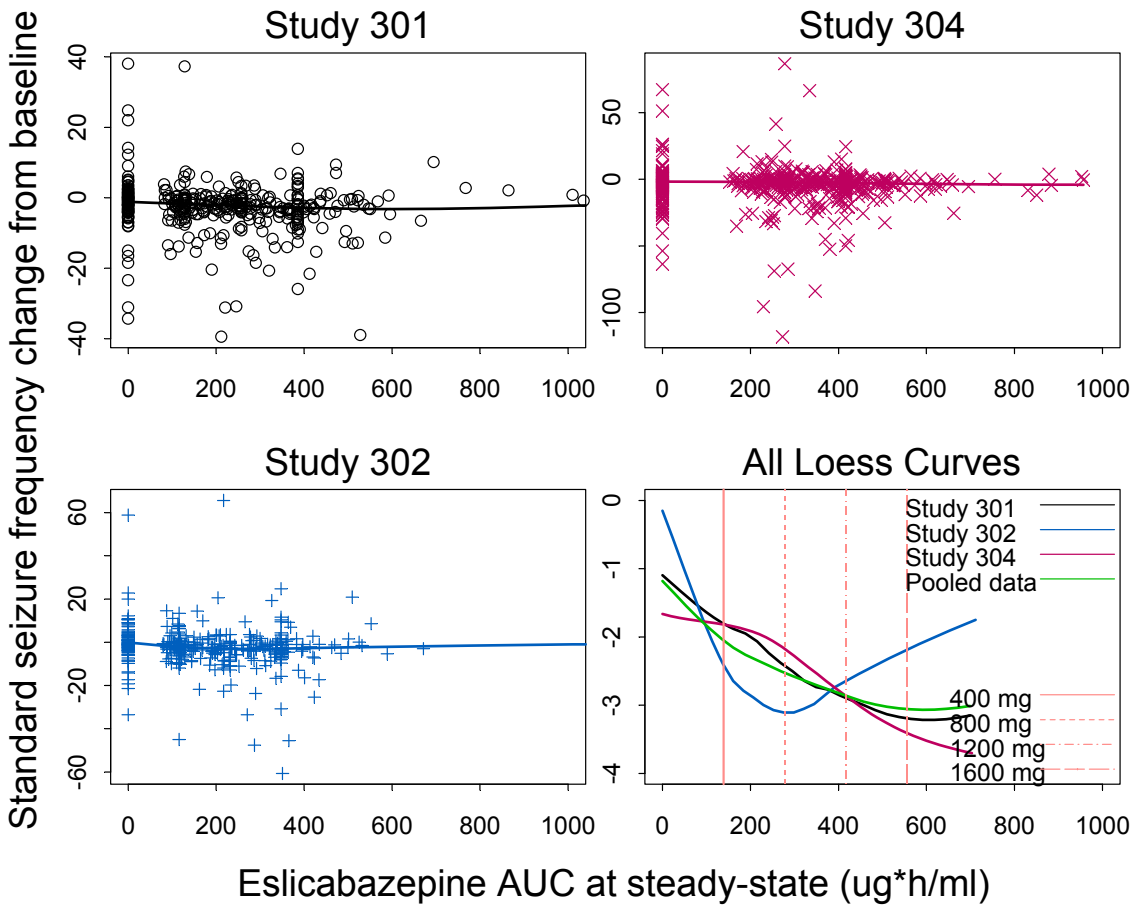
Corresponding to population EC_{50} (SE) of 15.7 (17.3) mcg/mL, the population mean ED_{50} (SE) is 301 (410) mg QD. The high SE values suggest large inter-subject variability in the drug effect.

Figure 8: The fitting curve versus observed data for the secondary efficacy endpoint



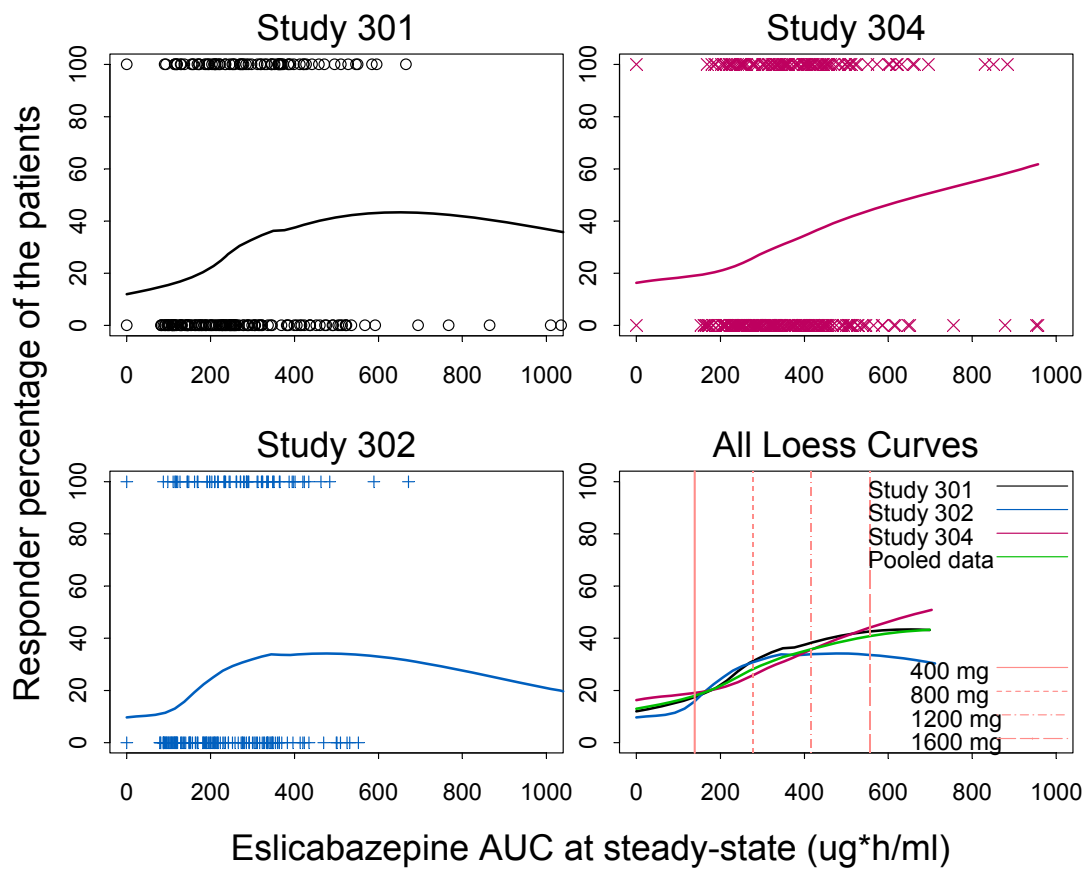
For each individual study, observed primary efficacy and secondary efficacy data for individual subjects, together with loess curves, are presented in Figure 9 and Figure 10. High inter-study variability was observed.

Figure 9: The relationship between standard seizure frequency change from baseline and eslicarbazepine exposure in scatter plots with loess curves for Phase III Studies BIA-2093-301, BIA-2093-302 and BIA-2093-304



Reference ID: 3374277

Figure 10: The relationship between responder rate and eslicarbazepine exposure in scatter plots with loess curves for in Phase III Studies BIA-2093-301, BIA-2093-302 and BIA-2093-304



Reference ID: 3374277

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEI YU
09/16/2013

HONGSHAN LI
09/16/2013

VENKATESH A BHATTARAM
09/16/2013

YUXIN MEN
09/16/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22416	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 11, 2013		
Division:	Division of Neurology Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Sunovion Pharmaceuticals Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	To be determined	**Date Assigned:**	February 11, 2013
Generic Name:	Eslicarbazepine Acetate Tablets	**Date of Review:**	August 27, 2013
Indication:	Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older	**Type of Submission:** 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Immediate release tablet/ 200 mg/tablet, 400 mg/tablet, 600 mg/tablet, and 800 mg/tablet		
Route of Administration	Oral		

SUMMARY

Submission:

The proposed drug product is an immediate release tablet containing eslicarbazepine acetate as the active ingredient, indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older. This 505(b)(1) New Drug Application was originally submitted on 3/30/2009 for the 400 mg/tablet, 600 mg/tablet, and 800 mg/tablets strengths, and received a complete response letter on 4/30/2010, due to clinical concerns. On 9/4/2012 the Applicant resubmitted the NDA and included the addition of a 200 mg/tablet strength. The first resubmission was considered an incomplete response as stated in a letter from the FDA dated 11/2/12. Therefore, the Applicant submitted a second resubmission to the NDA dated 2/11/13, which is the subject of this review.

Review:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

1) the proposed dissolution methodology,
2) the dissolution acceptance criteria
3) the biowaiver request for the lower 200 mg strength
4) the bridging of the formulations and manufacturing sites
5) (b) (4) and
6) 200 mg tablet splitting

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RECOMMENDATION:

- The following dissolution method and acceptance criteria are acceptable for the 400mg, 600mg, 800mg tablets:

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Eslicarbazepine acetate	IR Tablet	USP 2 (Paddle)	100	1000 mL pH 4.5 acetate buffer at 37°C	(b) (4) (Q) after 15 minutes and (b) (4) (Q) after 45 minutes

- The dissolution profile comparison data do not support the approval of the biowaiver request for the 200 mg tablet and therefore is NOT granted. From the Biopharmaceutics perspective the proposed 200 mg strength tablet is NOT acceptable.

- The results from the dissolution study evaluating the (b) (4) indicate that (b) (4) product have different dissolution rates (failed f_2 test). Therefore, the results from the clinical studies (e.g. double blind placebo controlled trials) (b) (4) maybe affected. The impact of a possible bias on the overall clinical (safety and efficacy) results when (b) (4) was administered would need to be further assessed by the Medical Reviewer.

- The provided data support the splitting of the 200 mg tablets. However, since the 200 mg lower strength is NOT recommended for approval, the splitting of the 200 mg tablets is irrelevant.

From the Biopharmaceutics perspective, NDA 22416 for Eslicarbazepine Acetate Tablets containing **400 mg, 600 mg, or 800 mg** eslicarbazepine acetate per tablet is recommended for **APPROVAL**. **The 200 mg eslicarbazepine acetate per tablet is not recommended for approval.**

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

The proposed drug product is an immediate release tablet containing eslicarbazepine acetate as the active ingredient, indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older. The main metabolite of eslicarbazepine acetate is eslicarbazepine which is responsible for the pharmacological effect. Eslicarbazepine acetate is classified as a very slightly soluble compound based on the solubility in aqueous solvents. Results from apparent permeability determinations indicate that eslicarbazepine acetate is a highly permeable compound that is easily absorbed by an apparent passive transport. This 505(b)(1) New Drug Application was originally submitted on 3/30/2009 for the 400 mg/tablet, 600 mg/tablet, and 800 mg/tablets strengths, and received a complete response letter on 4/30/2010, due to clinical concerns. During the first review cycle, the CMC review for the original NDA recommended approval. Note that there was no separate Biopharmaceutics review for the original NDA and the dissolution method and acceptance criteria for this product were approved in the CMC review.

The following dissolution method and acceptance criteria were found acceptable for the 400 mg/tablet, 600 mg/tablet, and the 800 mg/tablet strengths during the first review cycle (*refer to the CMC review by Dr. Charles Jewell dated 3/3/2010 in DARRTS*).

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Eslicarbazepine acetate	IR Tablet	USP 2 (Paddle)	100	1000 mL pH 4.5 acetate buffer at 37°C	(b) (4) (Q) after 15 minutes and (b) (4) (Q) after 45 minutes

During the original CMC review, splitting of the 600 mg and 800 mg tablets was found acceptable; (b) (4) The Applicant (b) (4) develop a 200 mg tablet. On 9/4/2012, the Applicant resubmitted the NDA, which included 17 new clinical studies, updated CMC and nonclinical information, new bioequivalence studies, and the addition of a 200 mg/tablet strength. The first resubmission was considered to be incomplete and received a Refuse to File (RTF) action as stated in a letter from FDA dated 11/2/12. Therefore, on 2/11/13, the Applicant submitted a second resubmission to the NDA dated 2/11/13, which is the subject of this review.

REVIEW:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:
1) the proposed dissolution methodology and acceptance criteria,

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2) the biowaiver request for the lower 200 mg strength
3) the bridging of the formulations and manufacturing sites,
4) (b) (4) and
5) 200 mg tablet splitting.

BIOPHARMACEUTICS INFORMATION:

Composition of the proposed drug product tablets:

Strength	***200 mg***	**400 mg**	**600 mg**	**800 mg**		
Component	**Quantity (mg/ tablet)**				**Function**	**Reference**
Eslicarbazepine acetate	***200.0***	400.0	600.0	800.0	Active substance	PT-QCMN1
Povidone (b) (4)	(b) (4)				(b) (4)	USP
Croscarmellose sodium						NF
(b) (4)						USP
Magnesium stearate						NF
Tablet weight (target in mg)	***233***	467	700	933		
(b) (4)						

All 4 proposed tablet strengths are (b) (4)
The 200 mg, 600 mg and 800 mg tablets are oblong, whereas the 400 mg tablets are circular. The Applicant claims that the drug product demonstrates linear and dose-proportional pharmacokinetics between doses of 200 mg and 1200 mg once daily.

DISSOLUTION METHOD:

The proposed dissolution method is the same as the method previously proposed and found acceptable under the first review cycle for the original NDA for the 400 mg, 600 mg, and 800 mg tablets:

Rotating paddle apparatus (apparatus 2)
Dissolution medium acetate buffer solution pH 4.50
Volume 1000 ml
Temperature 37.0 °C
Stirrer speed 100 rpm

A short description of the dissolution method development is provided in section 3.2.P.2 and describes the selection of the dissolution test conditions as follows:

Selection of apparatus:
USP dissolution apparatus 2 (paddles) was chosen due to its acceptance as a standard procedure

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for tablet formulations.

Selection of rotation speed:

Considering the low aqueous solubility of eslicarbazepine acetate, a 100 rpm rotation speed for the paddles was selected in order to provide dissolution of eslicarbazepine acetate (b) (4)

Selection of dissolution medium:

Since the aqueous solubility of eslicarbazepine acetate in the range between pH 1.2 and 7.4 is virtually constant, (b) (4) The aqueous solubility of eslicarbazepine acetate is less than 1 mg/ml. (b) (4) therefore a volume of 1000 ml was selected. (b) (4)

Discriminatory power of the method:

The discriminatory power of the dissolution procedure has been evaluated by demonstrating that the proposed dissolution test method has sufficient discriminatory power to distinguish between batches of eslicarbazepine tablets of the same strength but with small differences between them with respect to drug substance particle size, tablet hardness, and composition.

The impact on dissolution of the following parameters was evaluated:

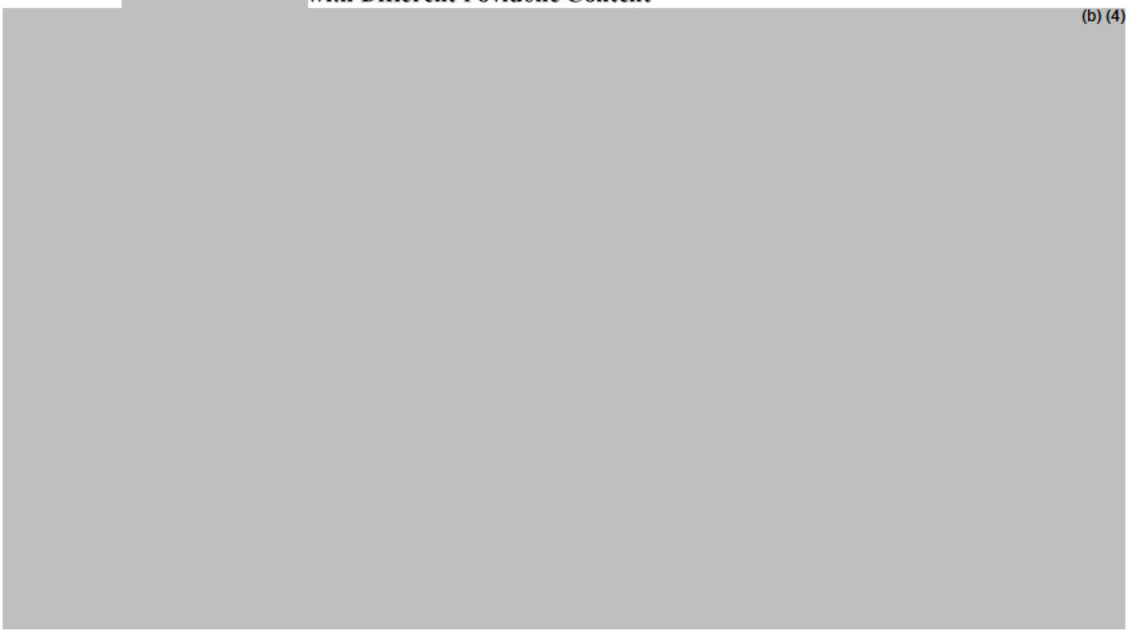
• Drug substance particle size:

Figure 8: Dissolution Profiles for Tablets Prepared with Different Eslicarbazepin Acetate Particle Size Fractions

(b) (4)

• Content of povidone:

Figure 10: Dissolution Profiles Obtained with Batches of Eslicarbazepine Acetate Tablets (b) (4) with Different Povidone Content



• Addition method for croscarmellose sodium:

Figure 11: Dissolution Profiles Obtained with Batches of Eslicarbazepine Acetate Tablets (b) (4) Differing in the Method used to Add the Croscarmellose Sodium

• Tablet hardness:

Figure 12: Dissolution Profiles Obtained with Batches of Eslicarbazepine Tablets (b) (4) Differing in Tablet Hardness

Reviewer's Overall Assessment on the dissolution method: Acceptable

The proposed dissolution method is the same as the method that was found acceptable for the 400 mg/tablet, 600 mg/tablet, and the 800 mg/tablet strengths during the first review cycle (refer to the CMC review of the original NDA). The Applicant adequately justified the selected dissolution apparatus, rotation speed, and dissolution medium. The discriminatory power of the dissolution method was demonstrated. The proposed dissolution method has previously found acceptable for the 400, 600, and 800 mg strength tablets; however, this method appears to be less than optimal for the 200 mg tablet, (b) (4)
The Applicant did not provide data showing the discriminating capability of the method for the 200 mg tablet.

DISSOLUTION ACCEPTANCE CRITERIA:

The proposed acceptance criteria for all strengths are the same as those previously accepted for the 400 mg/tablet, 600 mg/tablet, and the 800 mg/tablet strengths during the first review cycle:

(b) (4) (Q) after 15 minutes
and
(b) (4) (Q) after 45 minutes

Note that for the 200 mg the provided dissolution data (see table below) supports a dissolution criterion of Q= (b) (4) at 15 minutes.

The Applicant states that the proposed acceptance criteria are based on results from the following clinical and registration batches:

Formula	Strength (mg)	Batch	*PT-PTDPE9*	
			15 minutes (%)	45 minutes (%)
FP	*200*	*070221*	(b) (4)	
		070576		
		070577		
		080214		
		080215		
		090160		
		090161		
		100027		
		100295		
		100296		
		100297		
		100298		
		100849		
		100931		
		100932		
FN	400	030166-L		
		040029-L		
		040120-L		
		050058-L		
FP		050077-L		
		060156-L		
		PD269M-001		
		PD286M-001		
		PD286M-002		
		PD286M-003		
FK	600	030167-L		
		040121-L		
		050059-L		
FP		050076-L		
		060157-L		
		PD270M-001		
		PD287M-001		
		PD287M-002		
		PD287M-003		

Formula	Strength (mg)	Batch	*PT-PTDPE9*	
			15 minutes (%)	45 minutes (%)
FC	800	040013-L	(b) (4)	
		040030-L		
		040122-L		
		050007-L		
		050032-L		
		050052-L		
		050053-L		
		060179-L		
FP		050075-L		
		060158-L		
		PD271M-001		
		PD288M-001		
		PD288M-002		
		PD288M-003		

Note that the 200 mg tablets hav (b) (4)

Because of the low aqueous solubility of the drug substance, (b) (4) is proposed to control the particle size distribution in the drug product.

Mean dissolution profiles obtained for the drug product formulation FP using the proposed dissolution method are shown below:

Information request dated 6/13/13:

Provide comparative dissolution profiles for a 200 mg drug product batch with formulation FP, manufactured at (b) (4) *(CGGM, CGGN, or CGGP) and compare it to dissolution profiles of 400 mg, 600 mg, and 800 mg tablet batches with formulation FP that were used in clinical*

studies.

Applicant's response dated 6/28/13:

Multi point dissolution data are provided in Table 5 (200 mg and 400 mg strengths) and Table 6 (600 mg and 800 mg strengths) for the pivotal clinical and registration batches for the proposed commercial drug product (Formula FP) using the proposed dissolution method.

Table 5: Dissolution Data for Eslicarbazepine Acetate Tablets, 200 mg and 400 mg

Strength	200 mg			400 mg							
Purpose	Registration Batches						Pivotal Batches				
Lot	CGGM	CGGN	CGGP	PD286M-001	PD286M-002	PD286M-003	C8B0357	C9A2318	DVWS	C9J2011	CVXN
Vessel	15 Minute Individual Vessel Dissolution Data % Assay										
1	(b) (4)										
2											
3											
4											
5											
6											
Mean											
SD											
	45 Minute Individual Vessel Dissolution Data %Assay										
1	(b) (4)										
2											
3											
4											
5											
6											
Mean											
SD											

Table 6: Dissolution Data for Eslicarbazepine Acetate Tablets, 600 mg and 800 mg

Strength	600 mg			800 mg			
Purpose	Registration Batches						Pivotal Batch
Lot	PD287M-001	PD287M-002	PD287M-003	PD288M-001	PD288M-002	PD288M-003	PD271M-001
Vessel	15 Minute Individual Vessel Dissolution Data % Assay						
1	(b) (4)						
2							
3							
4							
5							
6							
Mean							
SD							
Vessel	45 Minute Individual Vessel Dissolution Data %Assay						
1	(b) (4)						
2							
3							
4							
5							
6							
Mean							
SD							

Assessment of the response:
The provided dissolution data are not the requested dissolution profile data, since only two points are covered (15 and 45 minutes), and not the full profile (e.g., 10, 15, 20, 30, 45, and 60 minutes).

Follow up information request dated 7/11/13:
Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figures and tables containing individual data, mean, and SD for a 200 mg drug product batch with formulation FP, manufactured at (b) (4) *(CGGM, CGGN, or CGGP) and compare it to dissolution profiles of 400 mg, 600 mg, and 800 mg tablet batches with formulation FP that were used in clinical studies (include batches used in the BIA-2093-130 clinical study). Provide f2 calculations for the comparisons.*

Applicant's response dated 8/1/13:
The requested data, figures, and tables were provided and indicate that a dissolution acceptance criterion of Q= (b) (4) *would be appropriate. However, there are no data available for the registration batches at this time point. Since the dissolution acceptance criteria were previously negotiated and agreed upon during the first review cycle, and since the stability data were collected at 15 and 45 minute time points based on the previously agreed dissolution acceptance criteria, the following previously agreed upon dissolution acceptance criteria still are acceptable for the 400 mg, 600 mg, and 800 mg tablets:*

Q (b) (4) after 15 minutes and Q (b) (4) after 45 minutes

Since the 200 mg tablet is NOT acceptable, dissolution acceptance criteria are not needed for strength. However, note that the dissolution data support a dissolution criterion of Q= (b) (4) *at 15 minutes for the 200 mg tablet.*

BRIDGING OF DIFFERENT FORMULATIONS:

(b) (4) . A schematic overview of the formulation development is depicted below:

(b) (4)

The pivotal phase 3 FC, FN and FK formulations were linked to the to-be-marketed, commercial FP formulation by comparative bioavailability studies. In addition to the formulation changes, a drug product manufacturing site change occurred during the drug product development. All drug product batches for formulations FA cel, FB emc, FC, FK, and FO are manufactured in BIAL. For the final to-be-marketed commercial FP formulation, there are drug product batches of each strength that were manufactured in (b) (4) as well as in BIAL. Clinical trials, including BA studies, for the 400, 600 and 800 mg tablets used drug product batches from both manufacturing sides. However, clinical trials for the 200 mg tablets only used drug product batches manufactured in BIAL. There are no BA data available for to-be-marketed FP formulation of the 200 mg tablets manufactured by (b) (4). In an attempt to demonstrate (in vitro) equivalence between the two manufacturing sites, the Applicant has submitted comparative dissolution profiles between 200 mg FO (manufactured in BIAL) and 200 mg FP (manufacturing site was not specified). In order to bridge the two manufacturing sites for the 200 mg FP tablets, the Applicant was asked to provide the following comparative dissolution profiles:

Information request dated 6/13/13:
It appears that you do not have BA/BE data for the 200 mg drug product manufactured at (b) (4) *Therefore, you may request a Biowaiver for the 200 mg drug product including a justification, raw dissolution data and comparative dissolution profiles between:*

-The 200 mg drug product, formulation FP, manufactured at (b) (4) *and*
-The 400 mg and/or 800 mg tablets with formulation FP used in the BIA-2093-130 clinical study

Applicant's response dated 6/28/13:
A formal request for a biowaiver for the eslicarbazepine acetate 200 mg tablets is provided in Module 1.12.15. In this module, the Applicant did not provide the requested raw dissolution data

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and comparative dissolution profiles between:

-The 200 mg drug product, formulation FP, manufactured at (b) (4)*, and*

-The 400 mg and/or 800 mg tablets with formulation FP used in the BIA-2093-130 clinical study

Follow up information request dated 7/11/13 see above:

Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figures and tables containing individual data, mean, and SD for a 200 mg drug product batch with formulation FP, manufactured at (b) (4) *(CGGM, CGGN, or CGGP) and compare it to dissolution profiles of 400 mg, 600 mg, and 800 mg tablet batches with formulation FP that were used in clinical studies (include batches used in the BIA-2093-130 clinical study). Provide f2 calculations for the comparisons.*

Applicant's response dated 8/1/13:

The requested data, figures, and tables were provided and can be summarized as follows:

Study	Strength	Reference Lot Number	pH	f_2 as compared to 200 mg Lot Number CGGM
BIA-2093-117	400-mg	PD269M-001	(b) (4)	25
BIA-2093-122				35
BIA-2093-130				36
BIA-2093-122	600-mg	PD270M-001		26
				35
				35
BIA-2093-117	800-mg	PD271M-001		23
BIA-2093-122				30
				30
BIA-2093-130	800-mg	TXB		28
				38
				36

The similarity factors are not greater than 50, indicating the *in vitro* dissolution profiles are not similar. Visual inspection of the dissolution profiles demonstrates that the 200 mg tablets dissolve (b) (4) the other tablet strengths. For example:

(b) (4)

Assessment of Applicant's response:
Based on the results of the provided comparative dissolution data showing failed similarity f2 values, a Biowaiver for the 200 mg tablets cannot be granted. Since the Applicant did not have BA or BE data for the proposed 200 mg drug product manufactured at (b) (4)*, this strength (200 mg) is NOT recommended for approval. The 200 mg tablet is intended for use as a titration dose for subjects with severe renal impairment. For those patients, a 400 mg every other day, instead of 200 mg daily dose, maybe considered.*

(b) (4)

Information request dated 6/13/13:
Provide a corrected Table 11 (pg 18/50 section P.2. drug product). The provided table appears to have several typographical errors.

The Applicant submitted the following corrected table on 6/28/13:

Strength (tablets per capsule)	[redacted] Tablets		[redacted] tablets	
	15 Minutes	45 Minutes	15 Minutes	45 Minutes
400 mg (One 400-mg)	[redacted]			
600 mg (One 600 mg)				
800 mg (Two 400-mg)				

[a] Data were updated in response to FDA Request for Information dated June 13, 2013.

Follow up information request dated 7/11/13 see above:
Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figures and tables containing individual data, mean, and SD for the 400, 600, and 800 mg [redacted] tablets. Provide f2 calculations for the comparisons.

Applicant's response dated 8/1/13:
The requested data, figures, and tables were provided and can be summarized as follows:

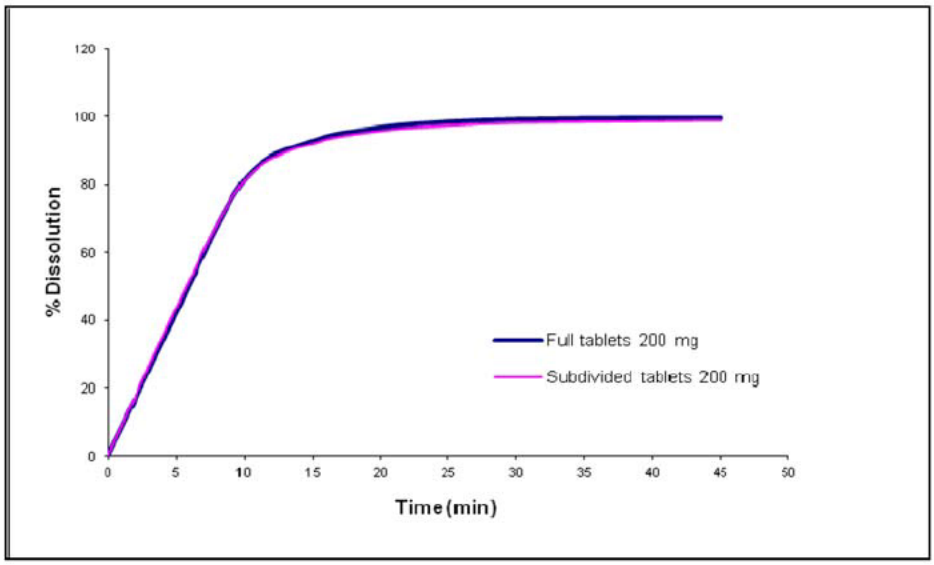
Strength	[redacted] Lot Number	[redacted] Lot Number	f_2
400 mg	C8B0357	146I1008	53
600 mg	C8J0107	169I1208	52
800 mg (2x400-mg)	C8B0357	147I1008	35

These comparative dissolution data indicate that results from the clinical studies (e.g. double blind placebo controlled trials) using [redacted] maybe bias. The impact of this possible bias on the safety and efficacy may need to be further assessed by the Medical Reviewer.

TABLET SPLITTING:

During the review of the original NDA tablet splitting was found acceptable for the 600 and 800 mg strengths, but not for the 400 mg strength. The newly proposed 200 mg strength tablet has a score and the acceptability of the score was tested by comparing the mean dissolution profiles (n=6). In addition, tests for divisibility and friability of the full and subdivided tablets were performed. Even though there is no proposed dose of 100 mg, from clinical perspective a score on the 200 mg tablet, giving the ability to split a 200 mg tablet in half, is useful for administering a 500 mg or 700 mg dose.

Figure 16: Mean Dissolution profiles of Full and Subdivided 200-mg Tablets



It was unclear whether this graph was obtained with full dissolution profile data or using only the 15 and 45 minute time points. Therefore the following information request was sent to the Applicant:

Information request dated 7/11/13:
Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figure and tables containing individual data, mean, and SD for the 200 mg intact and subdivided tablets used to create Figure 16. Provide f2 calculations for the comparison.

Applicant's response dated 8/1/13:
The requested data, figures, and tables were provided and it was shown that the two dissolution profiles are similar, based on an f_2 factor of 93.

Assessment of Applicant's response:
The provided data indicate that the proposed 200 mg tablet can be split. However, since the biowaiver cannot be granted, this Review recommends that the 200 mg tablets will not be approved.

OVERALL RECOMMENDATION:

- The following dissolution method and acceptance criteria are acceptable for the 400mg, 600mg, and 800mg tablets:

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Eslicarbazepine acetate	IR Tablet	USP 2 (Paddle)	100	1000 mL pH 4.5 acetate buffer at 37°C	(b) (4) (Q) after 15 minutes and (b) (4) (Q) after 45 minutes

Reference ID: 3364079

- Bridging of the strengths, manufacturing sites, formulations:
  Based on the provided comparative dissolution data, a biowaiver for the 200 mg tablets is NOT granted. Since there are no BA/ BE data to support the approval of the proposed 200 mg drug product manufactured at (b) (4) this strength (200 mg) is NOT recommended for approval.

- (b) (4)
  The results from the dissolution study evaluating the effect of (b) (4) product have different dissolution rates (failed f2 test). Therefore, the results from the clinical studies (e.g. double blind placebo controlled trials) using the (b) (4) maybe affected. The impact of a possible bias on the overall clinical (safety and efficacy) results (b) (4) would need to be further assessed by the Medical Reviewer. This issue was conveyed to the review team on 8/23/13.

- Tablet splitting of the 200 mg tablets:
  The provided data support the splitting of the 200 mg tablets. However, since the 200 mg lower strength is NOT recommended for approval, the splitting of the 200 mg tablets is irrelevant.

From the Biopharmaceutics perspective, NDA 22416 for Eslicarbazepine Acetate Tablets containing **400 mg, 600 mg, or 800 mg** eslicarbazepine acetate per tablet is recommended for **APPROVAL**. **The 200 mg eslicarbazepine acetate per tablet strength is NOT recommended for approval.**

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/s/

ELSBETH G CHIKHALE
08/27/2013

ANGELICA DORANTES
08/27/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission (Resubmission after RTF)

		Information		Information
NDA Number		22-416	Brand Name	Stedesa™
OCP Division (I, II, III, IV, V)		I	Generic Name	Eslicabazepine Acetate (SEP-0002093 or BIA 2-093)
Medical Division		120	Drug Class	• First-line dibenz[b,f]azepine antiepileptic • Voltage-gated sodium channel (VGSC) blocker
OCP Reviewers	CP	Bei Yu	Indication(s)	Adjunctive therapy in the treatment of partial-onset seizures in adults
	CP Team Leader (Acting)	Ta-Chen Wu		
	PM	Joo-Yeon Lee Atul Bhattaram		
	PG	None		
Date of Original Submission		3/29/09	Dosage Form	Tablets: 200, 400, 600, and 800 mg
Date of Resubmission		8/31/12	Dosing Regimen	Initial: 400 mg QD for 1 week Maintenance: 800 mg QD Maximum: 1200 mg QD Titration: increments of 400 mg at weekly internals
Estimated Due Date of OCP Review		1/4/13	Route of Administration	Oral
Medical Division Due Date		1/12/13	Sponsor	Sunovion
PDUFA Due Date		1/19/13	Priority Classification	S

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clin. Pharm. and Biopharm. Information

Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel and t-type calcium channel blocker with anticonvulsant activity. It was designed to constitute a third-generation, single-enantiomer member of the long established family of first-line dibenz[b,f]azepine antiepileptic drugs (AEDs) represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). It's a prodrug of eslicarbazepine, which is the drug entity responsible for the pharmacological effect.

The sponsor submitted the original NDA in March 2009 for the indication of "adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy". The agency issued the Complete Response Letter on April 30, 2010 due to profound and extensive deficiencies in the conduct and documentation of the study, as well in the presentation of the data in the application. OCP also provided specific comments in the letter, "You should consider developing a lower strength (200 mg) of Stedesa to allow everyday dosing during the titration phase in patients with severe renal impairment. Lower strengths are also appropriate for use in the elderly population."

From a clinical pharmacology perspective, the original NDA was acceptable based on the review by OCP reviewers Drs. Veneeta Tandon, Kofi Kumi, and Joo-Yeon Lee.

In the original NDA, there were 22 Phase I studies in healthy subjects or special populations, 2 Phase II studies (Studies 201 (b) (4)) and 3 Phase III studies (Studies 301, 302, and 303) (Ref: OCP NDA Filling and Review Form, NDA 22-416, Dr. Veneeta Tandon, 2009).

In the current resubmission (a response to 4/30/2010 CR letter), the sponsor submitted additional clinical pharmacology studies, among a total of 17 new clinical trials, in supportive of the 505(b)(1) route of approval, as listed below. A new Phase III study (2093-304 Part 1) conducted jointly by Sunovion and BIAL – Portela (Bial) to evaluate the safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures when given once daily at doses of 800 mg and 1200 mg.

BA/BE studies:
1. Study 093-155: a relative bioavailability and bioequivalence study comparing a crushed and an intact tablet of 800 mg SEP-0002093.
2. Study 2093-130: a bioequivalence study between a marketed formulation (MF) (Zebinix®) and a TBM formulation of SEP-0002093 at 2 dosage strengths (400 mg and 800 mg) to demonstrate equivalence with 2 active pharmaceutical ingredients (API) sources.

PK in healthy subjects:
1. MD study (Study 2093-127): CSF and plasma concentrations following ESL 600 mg QD for 3 days and 1200 mg QD for 6 days in Group A; OXC 300 mg BID for 3 days and 600 mg BID for 6 days in Group B.

PK in pediatric patients (children and adolescents, Phase IIa):
1. MD study (Study 2093-202): ESL suspension and tablets. 5 mg/kg/day QD for 4 wks, 15 mg/kg/day QD for 4 weeks, and 30 mg/kg/day QD for 4 weeks.

Extrinsic Factors (Drug Interactions):

1. Simvastatin (Study 2093-124)
2. Contraceptive (Study 2093-128)
3. Carbamazepine (Study 2093-129)
4. Rosuvastatin (Study 093-150)

In Vitro: 1. The sponsor also provided information based on in vitro dissolution profile studies to support a new 200 mg strength tablet (Section 3.2.P.2.2). The composition is (b) (4) between the strengths:

Table 1: Compositions of Eslicarbazepine acetate *200*, 400, 600 and 800 mg Tablets

Strength	***200 mg***	**400 mg**	**600 mg**	**800 mg**		
Component	**Quantity (mg/ tablet)**				**Function**	**Reference**
Eslicarbazepine acetate	***200.0***	400.0	600.0	800.0	Active substance	PT-QCMN1
Povidone (b) (4)					(b) (4)	USP
Croscarmellose sodium						NF
(b) (4)						USP
Magnesium stearate						NF
Tablet weight (target in mg)	***233***	467	700	933		
(b) (4)						

2. An in vitro study to evaluate the apparent permeability (Papp) of SEP-0002093 in Caco-2 cells (Document No. 093-535).

POP PK:

2 updated reports (e.g., DDI analysis between ESL and AEDs, such as levetiracetam, gabapentin, phenobarbital, and valproate)

PK/PD:

Study BIA-2093-123: effects of ESL (SD, 800, 900, and 1200 mg) on cognition and psychomotor function in healthy subjects.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			**9 reports for plasma and 2 reports for urine (original submission)**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	**x**	**1**		
Patients-				
single dose:				
multiple dose:	**x**	**1**		**Phase 3 study (Study 2093-304)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**x**	**4**		
In-vitro:	**x**	**1**		**Permeability study in Caco-2**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**	**1**		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**2**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**x**			
Total Number of Studies	**8 PK 1 IN VITRO 2 POP PK 1 PK-PD**			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Request to the sponsor:

1. Please clarify which API sources (new or current) of your drug products were used in Phase 1 and Phase 3 clinical studies in this application. It will be more helpful for you to provide us with a complete tabular listing of the new or current API source with the corresponding study.

2. Please provide the bioanalytical report for assay performance for Study 2093-129 as part of the NDA submission. You should provide adequate hyperlinks to the report and supporting data to facilitate the review process.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEI YU
12/26/2012

TA-CHEN WU
12/26/2012

Clinical Pharmacology Review

PRODUCT (Generic Name):	Eslicabazepine Acetate
PRODUCT (Brand Name):	STEDESA
NDA:	22-416
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	400, 600 and 800 mg
INDICATION:	Adjunct therapy in the treatment of Partial Onset Seizures in Adults
NDA TYPE:	1S
SUBMISSION DATES:	3/29/09
SPONSOR:	Sepacor
CP REVIEWER:	Veneeta Tandon, Ph.D. Kofi Kumi, Ph.D. (DDI Studies)
TEAM LEADER:	Angela Men, M.D., Ph.D.
PHARMACOMETRICS REVIEWER	Joo-Yeon Lee, Ph.D
PHARMACOMETRICS TEAM LEADER	Yaning Wang, Ph.D
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Eslicarbazepine acetate (also referred to as SEP-0002093 or ESL or BIA 2-093) tablets are proposed for the indication of "Adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy".

Eslicarbazepine acetate is a novel voltage-gated sodium channel blocker. It was designed as a third-generation, single-enantiomer member of the long-established family of first-line dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first generation) and oxcarbazepine (second-generation). It is a prodrug of eslicarbazepine, which is the drug entity responsible for the pharmacological effect. It is chemically related to carbamazepine and oxcarbazepine, but has been designed to prevent metabolism to toxic metabolites such as epoxides and the avoidance of enantiomeric

impurity and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates without losing anticonvulsant potency.

The chemical structure of eslicarbazepine acetate is S-(-)-10-acetoxy-10,11-dihydro-5Hdibenzo/ b,f/azepine-5-carboxamide. It shares with carbamazepine and oxcarbazepine 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, preventing the formation of toxic epoxide metabolites, such as carbamazepine-10,11 epoxide.

Eslicarbazepine acetate is an ester of S-licarbazepine (also called as eslicarbazepine). Following oral administration, eslicarbazepine acetate is rapidly and extensively metabolised to S-licarbazepine (eslicarbazepine, BIA 2-194), its major metabolite, and to R-licarbazepine (BIA 2-195) and oxcarbazepine, minor metabolites. The proportion of S-licarbazepine and R-licarbazepine following oral administration of eslicarbazepine acetate is 21:1; when oxcarbazepine is administered orally, the same metabolites (S-licarbazepine and R-licarbazepine) appear, but in a different proportion (4:1).

It is proposed to be marketed as 400, 600 and 800 mg uncoated tablets. The composition is [redacted] (b) (4) between the strengths, and [redacted] (b) (4) between the tablet strengths.

The SEP-0002093 clinical development program for the indication of adjunctive therapy in adults with partial-onset seizures included 23 Phase I studies in healthy subjects or special populations, two Phase II studies and three Phase III studies. In addition, three Phase II studies were performed in adults with bipolar disorder. In these studies, SEP-0002093 was administered to a total of 1667 subjects.

The Overall Clinical Pharmacology Summary is given in Section 1.3.

1.1 RECOMMENDATION

The NDA is acceptable from a Clinical Pharmacology perspective. The Labeling recommendations should be conveyed to the sponsor.

Comment to the Medical Officer:

Please see our recommdations regarding dosing in renal impaired patients on page 7-8.

1.2 PHASE IV COMMITMENT/REQUIREMNT

None

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Exposure-Response for Effectiveness:
There is a significant relationship between the primary endpoint (standardized seizure frequency) and steady-state average eslicarbazepine concentration (Cav-ss). This was also confirmed by two secondary analyses; responder analysis by the sponsor and percent reduction in standardized seizure frequency from baseline relative to the maintenance phase by the reviewer.

Exposure-Response for Safety:
Exposure-safety analyses have not been conducted. Most common adverse events were dizziness, headache, nausea, vomiting, somnolence, diplopia and abnormal coordination. A dose response was observed for these adverse events.

General Pharmacokinetics (ADME characteristics) of Eslicarbazpeine:
Absorption:

- SEP-0002093 or eslicarbazepine acetate is a prodrug of eslicarbazepine. Following oral administration, plasma concentrations of the prodrug usually remain at undetectable levels. It rapidly forms the major active metabolite (S)-licarbazepine or eslicarbazepine. The pharmacokinetics is mainly described in terms of this active species, which represents ~95% of overall plasma exposure.
- Peak plasma concentrations (C_{max}) of eslicarbazepine are attained 1-4 hours post-dose.
- Bioavailability is assumed to be high because the amount of metabolites recovered in urine corresponded to more than 90% of SEP-0002093 dose.

Distribution:

- The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent of concentration.
- Tissue distribution of eslicarbazepine is extensive, as evidenced by a high apparent volume of distribution (V_d/F), 188L.

Metabolism:

- SEP-0002093 is rapidly and extensively metabolized to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism in the presence of hydrolase. Eslicarbazepine corresponded to approximately 91% of the sum of all circulating drug entities (using AUC_{0-24} as a measure of systemic exposure) and to approximately 95% of the sum of the active compounds (SEP-0002093, eslicarbazepine, (R)-licarbazepine and oxcarbazepine).

- Minor metabolites in plasma are (R)-licarbazepine (4%) and oxcarbazepine (<1%), which are known to be pharmacologically active. Other metabolites that are pharmacologically inactive include the glucuronic acid conjugates of SEP-0002093, eslicarbazepine, (R)-licarbazepine and oxcarbazepine. Altogether, the plasma drug glucuronides (SEP-0002093-GLU, eslicarbazepine-GLU, (R)-licarbazepine-GLU, and oxcarbazepine-GLU) corresponded to only approximately 3% of total systemic drug exposure in healthy subjects.

Elimination:

- SEP-0002093 metabolites are eliminated from the systemic circulation, primarily by renal excretion, in the unchanged and glucuronide conjugate forms (two thirds (67%) in the unchanged form and one third (33%) after conjugation with glucuronic acid). In total, eslicarbazepine unchanged and its glucuronide form corresponds to 92% of total drug material excreted in urine.
- In healthy subjects, the renal clearance of eslicarbazepine (approximately 20 mL/min) is substantially lower than glomerular filtration rate (80-120 mL/min), suggesting that renal tubular reabsorption occurs.
- The apparent half-life of eslicarbazepine was 10-20 h and 13-20 h for healthy subjects and epileptic adult patients, respectively.

Single dose and multiple dose pharmacokinetics:

- Single dose pharmacokinetics was assessed on single ascending doses of 20-3600 mg.
- Steady-state plasma concentrations are attained after 4 to 5 days of once-daily dosing.

Dose proportionality:
The pharmacokinetics of eslicarbazepine are linear and dose-proportional, in both healthy subjects and patients, in the dose range of 400 to 1200 mg/day.

Pharmacokinetics in patients:
Pharmacokinetic in patients is similar to the healthy subjects.

Special Populations:
Renal Impairment:
The extent of systemic exposure (AUC0-∞) to eslicarbazepine was increased by 62%, 116% and 154% in the mild, moderate, and severe renal impairment group, respectively, in comparison to that of the healthy subjects. Dose reductions are recommended in the patients with moderate and severe renal impairment.

(b) (4)

The reviewer proposed dosing recommendations are as follows:

Dosing Recommendations	Normal (Clcr >80 ml/min)	Mild (Clcr 50-80 ml/min)	Moderate (Clcr 30-49 ml/min)	Severe (Clcr 15-29 ml/min)
Initial	400 mg QD Weekly increments to the next dose	400 mg QD Weekly increments to the next dose	300 mg QD Weekly increments to the next dose	200 mg QD Weekly increments to the next dose
Maximum	1200 mg QD	1200 mg QD	600 mg QD	600 mg QD

(b) (4)

This can be considered, because the lowest strength available is 400 mg. The 600 and 800 mg tablets are scored on one side and can be split, however, the 400 mg tablets is a small round tablets, the splitting of which is not feasible. Another consideration could be to develop a 200 mg tablet in the future as a Phase IV requirement. In the interim the 600 mg tablet could be split for use in the moderate renal impaired patients and the severe renal impaired patients (b) (4)

Repeated hemodialysis was effective in removing the SEP-0002093 metabolites from the systemic circulation.

Hepatic Impairment:
Moderate hepatic impairment did not affect the pharmacokientics of eslicarbazepine and dosage adjustment is not necessary. The pharmacokinetics of eslicarabazepine has not been evaluated in the severe hepatic impairment subjects.

Age:

Elderly: The pharmacokinetic profile of eslicarbazepine was unaffected in the elderly with creatinine clearance > 60 mL/min compared to the healthy subjects (18-40 years) after single and repeated doses. Therefore no dose adjustment is necessary in the elderly, if their creatine clearance is ≥ 60 ml/min.

Pediatrics: The pharmacokinetic in pediatrics is not evaluated at this time in patients < 18 years of age.

Gender: Pharmacokinetics of eslicarbazepine was not affected by gender. No dosage adjustment based on gender is necessary.

Race: Pharmacokinetics of eslicarbazepine was not affected by race (Caucasian n=534, Hispanic n=77, and Black n=12) based on a population analysis. There were few Asian

(N=6) to make adequate comparisons for this population. No dosage adjustment based on race is necessary.

Drug-drug Interactions:

- Eslicarbazepine is not a substrate of CYP isoenzymes.
- Eslicarbazepine is an inhibitor of CYP2C19.
- Eslicarbazepine is not an inducer of oral contraceptives and Phase II enzymes for glucuronidation and sulfation.

Effect of eslicarbazpeine on pharmacokinetics of other drugs:

Concomitant Drug	Effect	Dose Adjustment
Warfarin	23%↓ in S-warfarin AUC	Patients monitored and warfarin dose should be titrated to maintain INR
Oral Contraceptive	42%↓ in Ethinylestradiol AUC 37%↓ in Levonorgestrel AUC	Additional or alternative non-hormonal birth control should be used
Digoxin	none	none
Metformin	none	none

Effect of eslicarbazpeine on pharmacokinetics of AEDs:

Concomitant Drug	Effect on expousre	Dose Adjustment
Phenytoin	35%↑ in phenytoin AUC	Decrease Phenytoin dose
Lamotrigine Topirmate Carbamazpeine Valproate Levitiracetam Gabapentin	none	none

Effect of AEDs on pharmacokinetics of eslicarbazpeine:

Concomitant Drug	Effect on expousre	Dose Adjustment
Phenytoin	37%↓ in ESLI AUC	Higher eslicarabazepine dose may be needed
Carbamazepine	11-32% ↑ in ESLI CL/F	Higher eslicarabazepine dose may be needed
Phenobarbital	26% ↑ in ESLI CL/F	Higher eslicarabazepine dose may be needed
Valproate	8-26% ↓ in ESLI CL/F	none
Lamotrigine Topirmate Levitiracetam Gabapentin	none	none

Biopharmaceutics:

Formulations:
The 400, 600 and 800 mg tablets are [redacted] (b) (4)

BCS Class:
BCS Class has not been established. Eslicarbazepine acetate has very low aqueous solubility.

Bioequivalence/Relative Bioavailability:

- The to-be marketed tablet formulation (TBM) of Eslicarbazepine acetate is bioequivalent to the Tablet formulation used in the pivotal clinical trials (CTF: FC formulation) for all the proposed strengths of the Tablet (400, 600 and 800 mg)
- Oral suspension (50 mg/ml) is bioequivalent to the tablets.

Dosage Strength Equivalence:
2x400 mg to be marketed tablet is bioequivalent to 1x800 mg tablet.

Food Effect:
Food has no effect on the pharmacokinetics of eslicarbazepine.

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Kofi Kumi, Ph.D.
Division of Clinical Pharmacology I

Joo Yeon Li, Ph.D
Division of Pharmacometrics

Team Leader: Angela Men, M.D., Ph.D._____

Pharmacometrics Team Leader: Yanig Wang, Ph.D._____

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

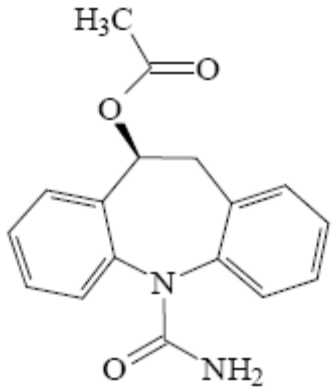
Dosage Form/Strengths/Route: Oral Uncoated Tablets, 400 (circular biconvex tablet), 600 and 800 mg (oblong tablet)

Indication: Adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy

Dosage and administration (Sponsor's Proposed):
Treatment should be initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily.

Pharmacologic Class: A voltage-gated sodium channel (VGSC) blocker with anticonvulsant property

Chemical Name: (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide. Mol Wt: 296.32



Other Names: SEP-0002093, BIA-2-093, eslicarbazepine acetate, ESL

Physical Characteristics: White to off-white, odourless crystalline solid. (b) (4)

Solubility: Very slightly soluble in aqueous solvents. Soluble in organic solvents such as acetone, acetonitrile and methanol. Insoluble in hexane.

Mechanism of action: In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through its active metabolite, eslicarbazepine. The precise mechanism(s) by which eslicarbazepine exerts its anticonvulsant actions are not fully characterized. However, *in vitro* electrophysiological studies indicate that eslicarbazepine stabilizes the inactivated state of voltage-gated sodium channels, preventing their return to the activated state resulting in an inhibition of repetitive neuronal firing. In addition, eslicarbazepine has been shown to inhibit T-type calcium channels which may contribute to its anticonvulsant effects.

Formulation: The composition per tablet for the 400, 600 and 800 mg strengths of eslicarbazepine acetate tablets that is proposed to be marketed is given in the following Table. The strengths are (b) (4)

Strength	**400 mg**	**600 mg**	**800 mg**		
Component	**Quantity (mg/ tablet)**			**Function**	**Reference**
Eslicarbazepine acetate	400.0	600.0	800.0	Active substance	PT-QCMN1
Povidone (b) (4)	(b) (4)				USP
Croscarmellose sodium					NF
(b) (4)					USP
Magnesium stearate					NF
Tablet weight (target in mg)	467	700	933		

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The SEP-0002093 clinical development program for the indication of adjunctive therapy in adults with partial-onset seizures included 23 Phase I studies in healthy subjects or special populations, 2 Phase II studies and 3 Phase III studies. In addition, three Phase II studies were performed in adults with bipolar disorder. In these studies, SEP-0002093 was administered to a total of 1667 subjects as shown in the Table below:

Table:	**Enumeration of Subjects in All Studies (Safety Population)**				
Study Type		**Placebo**	**SEP-0002093**	**Active Control**	**Total**
		(N)	**(N)**	**(N)**	**(N)**
Overall Unique Subjects[a]		501	1667	250	2010
Phase III Epilepsy Studies		289	840	0	1049
Phase II Epilepsy Studies		47	127	0	174
Phase II Bipolar Disorder Studies		51	252	0	303
Phase I Studies		115	532	255	596

Clinical Pharmacology Studies:
The 23 completed Phase I studies in the SEP-0002093 clinical program include: five bioavailability studies, two bioequivalence studies, six pharmacokinetic (PK) studies in healthy subjects, two PK studies in subjects with hepatic or renal failure, and seven studies assessing drug-drug interactions, one thorough QTc study.

One Phase II study was conducted in adults with partial seizures that aided in the design of Phase III studies. This study comprised of a 12-week double-blind treatment phase (no baseline period) followed by a 1-week tapering-off period. Both SEP-0002093 groups started at 400 mg and increased every 4 weeks by 400 mg to a maximum of 1200 mg.

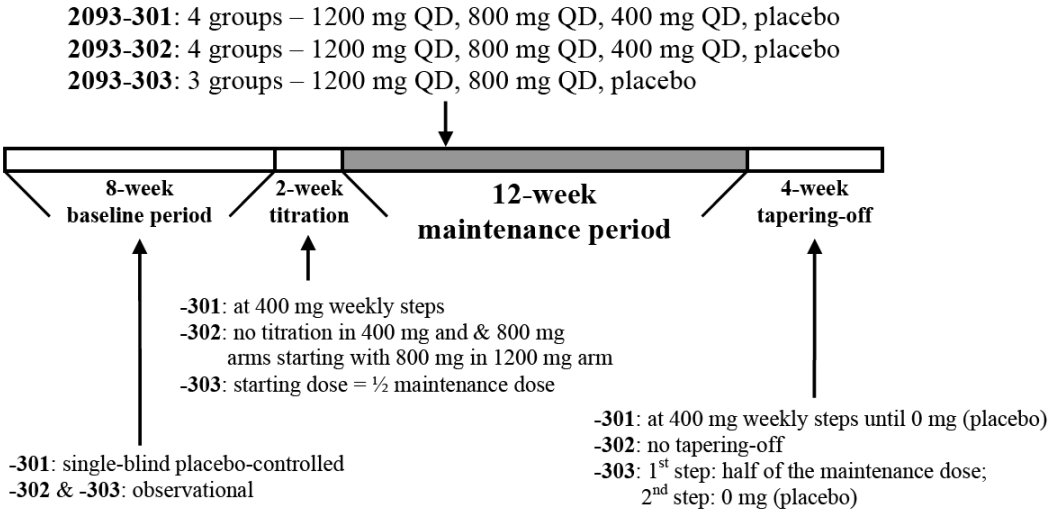
A second Phase II study (2093-202) was a pharmacokinetic study performed in children with partial refractory epilepsy. This study will help in future development of SEP-0002093 for pediatric patient populations, but is not subject to this NDA and has not been reviewed in detail.

Pivotal Clinical Studies:
Three Phase III studies were designed as multi-part, multicenter, randomized, double-blind, placebo-controlled studies in adults with refractory simple or complex partial seizures, with or without secondary generalization.

All Phase III studies included 2 parts. Part 1 of each study comprised an 8-week baseline period, a 2-week titration period, and a 12-week maintenance period with a 4-week

tapering-off period included in two of the three studies. Part 2 was a 1-year open-label extension phase to permit additional therapy for subjects deriving benefit from treatment. The schematic of Study design is given in the following Figure:

Figure: Summary of Part I of the Phase III studies (2093-301, 2093-302, and 2093-303)



The differences between studies include:

- There were three SEP-0002093 dose groups (400 mg, 800 mg or 1200 mg QD) in Studies 2093-301 and 2093-302, and two SEP-0002093 dose groups (800 mg or 1200 mg QD) in Study 2093-303
- The baseline period was observational in Studies 2093-302 and 2093-303, and was single-blind placebo in study 2093-301
- In study 2093-302 there was no tapering-off period.
- All three studies used slightly different titration and tapering-off regimens

Studies 2093-301 and 2093-302 which included a total of 795 subjects [202 placebo, 593 SEP-0002093 (196 at 400 mg, 198 at 800 mg, and 199 at 1200 mg)] represent pivotal adequate and well-controlled studies for the basis of the evaluation of efficacy. The long-term treatment effects of SEP-0002093 are available from the 1-year treatment extension phase of Study 2093-301 (Part 2).

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the three Phase III studies was standardized seizure frequency per 4 weeks over the 12-week maintenance period. The primary analysis was an analysis of covariance (ANCOVA) in the Intent-to-Treat (ITT) data set, including baseline seizure frequency as covariate in each of the pivotal studies, and additional number of baseline AEDs in study as covariates for the integrated analysis. Analysis of

the primary endpoint was also conducted in patient subgroups based on age, sex, race, body mass index, duration of epilepsy, age at diagnosis, worst seizure type at baseline, number and type of concomitant AED, and region to evaluate the consistency of the results across subpopulations.

Secondary endpoints were (a) the relative change (%) in standardized seizure frequency from baseline to the 12-week maintenance period and (b) the proportion of responders (defined as a patient with a ≥50% reduction in standardized seizure frequency from the 8-week baseline period to the 12-week maintenance period).

2.2.3 What are the characteristics of exposure/effectiveness relationships?

There is a significant relationship between the primary endpoint (standardized seizure frequency) and steady-state average eslicarbazepine concentration (Cav-ss), which was also confirmed by two secondary analyses; responder analysis by the sponsor and percent reduction in standardized seizure frequency from baseline relative to the maintenance phase by the reviewer.

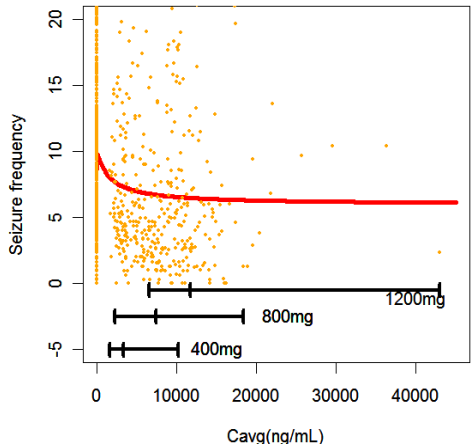
The two phase III studies (BIA-2093-301, BIA-2093-302) were included in the exposure-response analyses. The doses of 400mg, 800mg and 1200mg were compared to placebo in both studies. Both studies failed to show statistically that 400mg group is significantly better than placebo group in the efficacy analyses with respect to all endpoints including primary endpoint. The sponsor performed exposure-response analysis using two endpoints (standardized seizure frequency and responder rate) as the response variables and a predicted steady-state average eslicarbazepine concentration as an exposure.

The primary endpoint, seizure frequency, was defined as total standardized seizure frequency/28 days at maintenance phase. The values for this endpoint were log transformed prior to analysis. Since some patients reported no observed total standardized seizure frequency/28 days during the maintenance phase, the value of 4 was added to all seizure frequencies prior to log transformation.
The secondary endpoint, a responder was defined as a patient with at least 50% reduction in standardized seizure frequency from baseline relative to the maintenance phase (1 = responder, 0 = non-responder).

In addition to that, the reviewer evaluated the relationship using a different endpoint, relative change in seizure frequency from baseline, which is a typical primary endpoint for this indication.

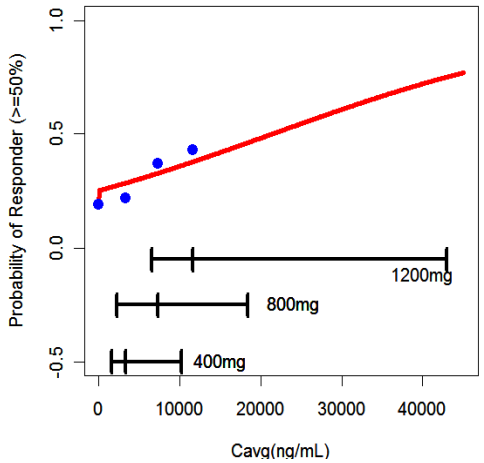
The sponsor's analyses showed a significant relationship in both endpoints, which was also confirmed by the reviewer's independent analysis (see Figures A, B and C).

Figure A. The relationship between standardized seizure frequency and Cavss.



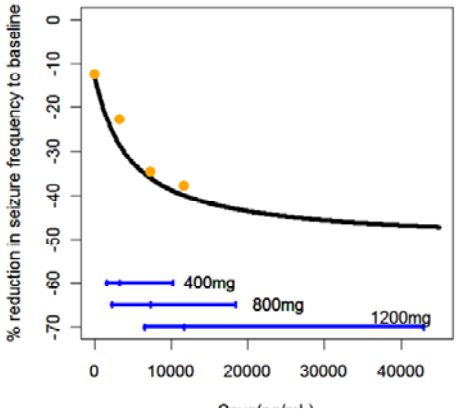
The orange dots represent observed data and red solid line indicates the model predicted relationship. Each horizontal line is the range of exposure (Cavss) at each dose group.

Figure B. Probability of responder .vs.eslicarbazepine Cavss.



The blue dots represent the observed Probability at each quartile of eslicarbazepine Cavss and the red solid line is the model-predicted probability of responder. Each black horizontal bar indicates the range of Cavss at each dose group.

Figure C. Model-predicted relationship between relative change (%) in seizure frequency and steady-state average concentration.



The orange dots indicate the observed percent reduction at the median Cavss of each dose group and the black solid line represents model-predicted relationship. Each horizontal line is the range of exposure (Cavss) at each dose group.

2.2.4 What are the characteristics of exposure-safety relationships?

Exposure-safety analyses have not been conducted. Most common adverse events were dizziness, headache, nausea, vomiting, somnolence, diplopia and abnormal coordination. A dose response was observed for these adverse events.

2.2.5 Does eslicarbazepien acetate prolong QT or QTc interval?

No significant QT prolongation effect of eslicarbazepine acetate (1200 mg and 2400 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between eslicarbazepine acetate (1200 mg and 2400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

Table: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Eslicarbazepine Acetate (1200 mg and 2400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Eslicarbazepine Acetate 1200 mg	12	1.5	(-1.0, 3.9)
Eslicarbazepine Acetate 2400 mg	23.5	1.4	(-1.2, 4.1)
Moxifloxacin 400 mg*	2	12.0*	(9.5, 14.5)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 6 timepoints is 8.3 ms.
For details please refer to IRT review.

2.2.6 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Following oral administration, SEP-0002093 or ESL is rapidly and extensively biotransformed to eslicarbazepine (S-licarbazepine, BIA 2-194) by first pass hydrolytic metabolism. When a chiral method is used, the assay is able to distinguish between eslicarbazepine and its R-enantiomer (R-licarbazepine, BIA 2-195), a minor metabolite. When an achiral method is used, it does not allow the separation of eslicarbazepine and R-licarbazepine, and the enantiomeric mixture has been reported as BIA 2-005. Both methods have been used for the assay of samples from clinical trials in healthy subjects and patients.

Assay validation for SEP-0002093, Eslicarbazepine, R-licarbazepine and oxcarbazepine were adequate (see Section 2.6).

2.2.7 What are the general ADME characteristics of Eslicarbazepine acetate?

The key ADME characteristics of eslicarbazepine acetate/eslicarbazepine are summarized below:

Absorption:

- SEP-0002093 or eslicarbazepine acetate is a prodrug of eslicarbazepine. Following oral administration, plasma concentrations of the prodrug usually remain at undetectable levels. It rapidly forms the major active metabolite (S)-licarbazepine or eslicarbazepine. The pharmacokinetics are mainly described in terms of this active species, which represents ~95% of overall plasma exposure.
- Peak plasma concentrations (C_{max}) of eslicarbazepine are attained 1-4 hours post-dose.
- Bioavailability is assumed to be high because the amount of metabolites recovered in urine corresponded to more than 90% of SEP-0002093 dose.
- Food has no effect on the pharmacokinetics of eslicarbazepine.

Distribution:

- The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent of concentration.
- Tissue distribution of eslicarbazepine is extensive, as evidenced by a high apparent volume of distribution (V_d/F), 188L.

Metabolism:

- No mass balance study was conducted. Fate of the drug was assessed in healthy subjects based on percentage of overall exposure in plasma and percent of the dose in the urine. Plasma and urine samples were taken upto 96 hours post dose to assess SEP-0002093 and its metabolites including the glucuronides.
- SEP-0002093 is rapidly and extensively metabolized to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism in the presence of hydrolase. Eslicarbazepine corresponded to approximately 91% of the sum of all circulating drug entities (using AUC_{0-24} as a measure of systemic exposure) and to approximately 95% of the sum of the active compounds (SEP-0002093, eslicarbazepine, (R)-licarbazepine and oxcarbazepine).
- Minor metabolites in plasma are (R)-licarbazepine (4%) and oxcarbazepine (<1%), which are known to be pharmacologically active. Other metabolites that are pharmacologically inactive include the glucuronic acid conjugates of SEP-0002093, eslicarbazepine, (R)-licarbazepine and oxcarbazepine. Altogether, the plasma drug glucuronides (SEP-0002093-GLU, eslicarbazepine-GLU, (R)-licarbazepine-GLU, and oxcarbazepine-GLU) corresponded to only approximately 3% of total systemic drug exposure in healthy subjects.

Elimination:

- SEP-0002093 metabolites are eliminated from the systemic circulation, primarily by renal excretion, in the unchanged and glucuronide conjugate forms: two thirds (67%) in the unchanged form and one third (33%) after conjugation with glucuronic acid. In total, eslicarbazepine unchanged and its glucuronide form corresponds to 92% of total drug material excreted in urine.
- In healthy subjects, the renal clearance of eslicarbazepine (approximately 20mL/min) is substantially lower than glomerular filtration rate (80-120 mL/min), suggesting that renal tubular reabsorption occurs.
- In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 h and 13-20 h, respectively.

The sponsor proposed metabolic pathway and the fate of the drug is shown in the following Figure:

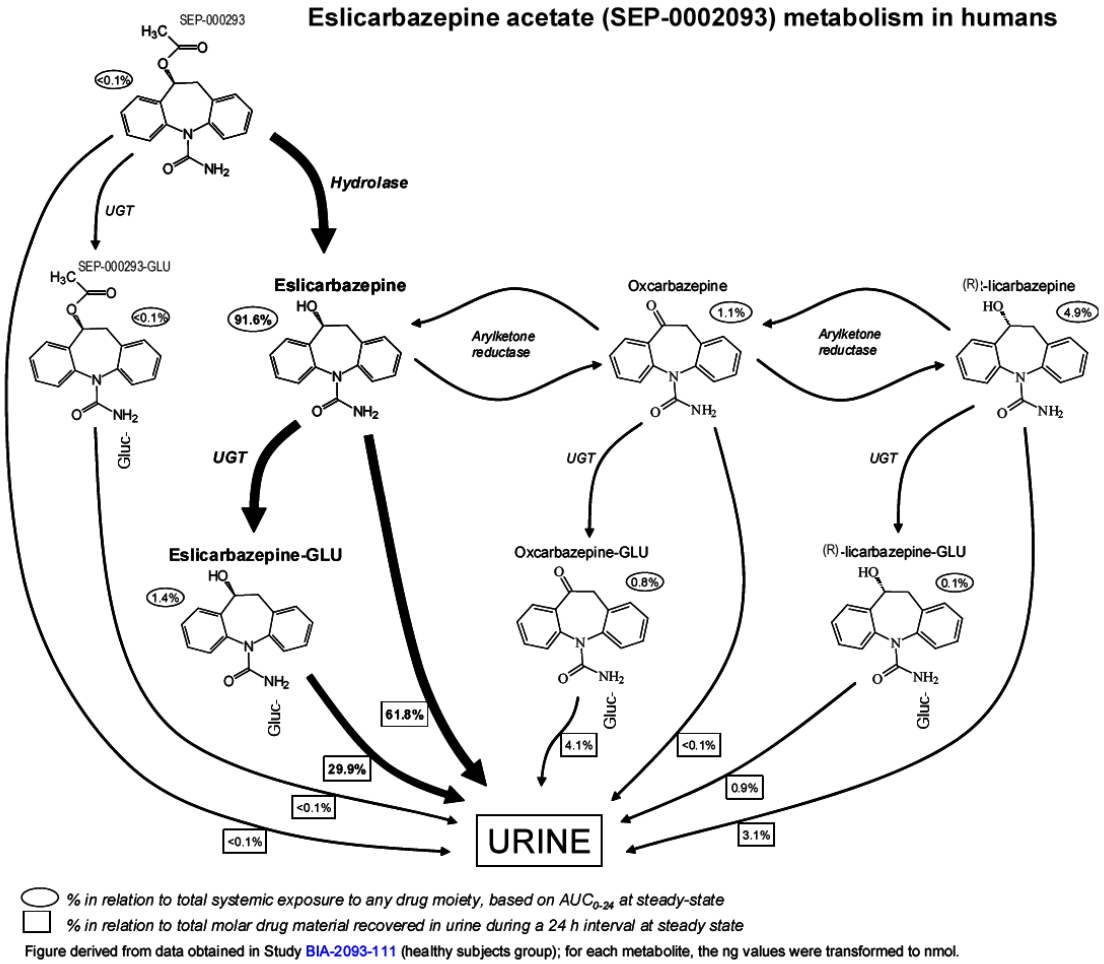


Figure derived from data obtained in Study BIA-2093-111 (healthy subjects group); for each metabolite, the ng values were transformed to nmol.

2.2.8 What are the basic pharmacokinetic parameters of Eslicarbazepine after single and multiple doses?

Single Dose Pharmacokinetics:

Single dose pharmacokinetics was assessed on single ascending doses of 20-3600 mg in the healthy subjects. The plasma concentrations of SEP-0002093 were generally below the limit of quantitation in almost all subjects. Initial clinical pharmacology studies were conducted using achiral assay, hence -R and –S forms have been determined together and is referred to as BIA 2-005 or (RS)-licarbazepine. Oxcarbazepine consisted of <1% of exposure. The pharmacokinetic parameters for (RS)-licarbazepine or BIA 2-005 in the therapeutic dose range is given in the following Table.

Table: Mean (CV%) Pharmacokinetic Parameters of (RS)-licarbazepine Following Oral Administration of single dsoes of 400, 600, 900, and 1200 mg SEP-0002093

SEP-0002093	(RS)-licarbazepine				
Dose (mg)	**C_{max} (ng/mL)**	**t_{max} (h)**	**$AUC_{0-\tau}$ (ng·h/mL)**	**$t_{1/2}$ (h)**	**CL_R (mL/min)**
400	5,193 (11.6)	4 (4-5)	81,536 (10.8)	11.7 (18.6)	16.2* (17.5)
600	8,489 (20.0)	4 (0.5-5)	119,717 (17.4)	12.3 (14.8)	18.4* (18.8)
900	14,595 (18.2)	2.25 (0.75-4)	210,281 (10.6)	16.3 (31.9)	18.9 (14.3)
1200	18,579 (16.3)	4 (2-6)	285,626 (16.7)	16.5 (6.83)	15.9 (21.1)

t_{max} values are median with range of values in parentheses
n=6 per dose group; * n=5

After single doses of SEP-0002093, on average, maximum plasma concentrations of (RS)-licarbazepine were attained (t_{max}) at 4 h post-dose. Thereafter, plasma (RS)-licarbazepine concentrations declined in a multiphasic manner with a mean apparent terminal half-life ($t_{½}$) of approximately 8 to 17 h. The renal clearance of (RS)-licarbazepine was approximately 20 mL/min, which is low compared with glomerular filtration rate (127 mL/min), suggesting renal tubular reabsorption.

Multiple Dose Pharmacokinetics:

Multiple dose pharmacokinetics was assessed with 8 days dosing of 400 mg to 1200 mg in healthy subjects. In addition to this, repeat dosing of 1800 and 2400 mg was also assessed in a separate study. The pharmacokinetic parameters of (RS)-licarbazepine after multiple dosing within the therapeutic range is shown in the following Table. This Table also shows the single dose parameters at these doses on Day 1.

Table : Mean (CV%) Pharmacokinetic Parameters of (RS)-licarbazepine

Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng · h/mL)	$t_{½}$ (h)	R_0 (ratio)	CL_R (mL/min)
Day 1						

200 BID	3086 (43.5)	2 (0.5-4)	22,163 (28.0)	8.42# (26.8)	-	26.2 (20.6)
400 QD	7,827 (16.8)	1.75 (1-4)	96,262 (17.7)	12.7* (32.5)	-	21.7 (34.4)
800 QD	11,074 (17.3)	3 (1.5-7)	159,492 (13.6)	21.4* (60.4)	-	27.8 (27.9)
1200 QD	16,071 (13.9)	1.75 (1-7)	250,426 (10.9)	15.8* (15.1)	-	28.9 (23.0)
Day 8						
200 BID	6,683 (23.6)	2.75 (1-4)	63,140 (12.7)	9.40 (16.7)	2.95 (16.9)	23.2 (14.9)
400 QD	8,824 (16.0)	3 (0.5-7)	126,308 (11.7)	9.50 (18.8)	1.36 (28.3)	26.2 (32.1)
800 QD	18,675 (14.0)	2.5 (1-7)	268,384 (10.3)	12.3 (22.9)	1.70 (11.4)	20.9 (24.0)
1200 QD	25,457 (10.8)	3 (0.5-6)	423,003 (10.9)	13.1 (20.1)	1.70 (10.8)	27.0* (18.8)*

N=6 per dose group unless noted *n=5, #n=3

After multiple doses, on average (RS)-licarbazepine t_{max} was attained at 2 – 3 h post-dose, after which the plasma (RS)-licarbazepine concentrations declined with a mean apparent $t_{½}$ of approximately 9 – 13 h.
The mean pharmacokinetic parameters for oxcarbazepine are shown in the Table below:

Table: Mean (CV%) Pharmacokinetic Parameters of Oxcarbazepine

Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	$t_{1/2}$ (h)	R_0 (ratio)
Day 1					
200 b.i.d.	26.7	7	208	5.51*	-
	(30.0)	(1.5-8)	(30.8)	(32.2)	-
400 o.d.	59.2	6.5	849	8.04**	-
	(10.7)	(1-8)	(11.8)	(15.4)	-
800 o.d.	126	6	1840	9.24*	-
	(15.3)	(6-7)	(13.1)	(10.7)	-
1200 o.d.	197	6	2685	8.10#	-
	(43.6)	(1.5-8)	(15.6)	(22.1)	-
Day 8					
200 b.i.d.	78.2	7	698	12.7	3.38
	(43.2)	(1.5-7)	(35.7)	(18.6)	(14.1)
400 o.d.	102	3	1488	14.2	1.79
	(15.2)	(1-6)	(27.2)	(17.5)	(33.5)
800 o.d.	227	6	3464	13.3	1.85
	(28.6)	(1.5-6)	(33.5)	(13.1)	(21.7)
1200 o.d.	376	5	5480	14.1	2.05
	(19.6)	(1-8)	(19.1)	(10.6)	(16.5)

t_{max} values are median with range of values in parentheses
n=6 per dose group unless otherwise noted: * n=5, ** n=4, # n=2

Maximum plasma concentrations of oxcarbazepine were reached on average 3 to 7 h post-dose. Plasma concentrations of oxcarbazepine declined with an approximate mean apparent terminal half-life of 6 to 9 h following a single dose and 13 to 14 h following repeated administration.

2.2.9 Do the pharmacokinetic parameters change with time following chronic dosing?

(RS)-licarbazepine accumulated in plasma following repeated administration of SEP-0002093. Mean observed accumulation ratio (R_0) was 3.0 after repeated BID dosing, and 1.4 – 1.7 after QD dosing of 400-1200 mg. The accumulation ratio (R_0) for (RS)-licarbazepine following multiple-dose administration of 1800 mg and 2400 mg of SEP-0002093 in Study 113 was 1.47 and 2.13, respectively. Steady-state plasma (RS)-licarbazepine concentrations were attained at 4 – 5 days.

2.2.10 What is the variability in the PK data?

The inter-individual variability was from about 15-28% across the therapeutic doses.

2.2.11 How do the pharmacokinetics of the drug in healthy volunteers compare to that in epilepsy patients?

The pharmacokinetics of eslicarbazepine, R-licarbazepine and oxcarbazepine in patients was similar to the healthy subjects after multiple doses. The pharmacokinetics in patients was evaluated in a subset of patients from the Phase 3 study. The pharmacokinetic parameters in patients within the therapeutic dose range are given in the Table below:

Table: Pharmacokinetic parameters in patients:

	ESL dose	**C_{max}** (ng/mL)	**t_{max}** (h)	**AUC_{0-24}** (ng.h/mL)	**$t_{1/2}$** (h)
Eslicarbazepine (BIA 2-194)	400 mg (n=7)	9673 (5142)	2.0 (1.0-6.0)	132514 (89477)	12.8 (5.1)
	800 mg (n=26)	15462 (5000)	2.0 (1.0-6.0)	205359 (74584)	13.5 (6.1)
	1200 mg (n=18)	22957 (5263)	2.5 (1.0-6.0)	336147 (81654)	20.2 (10.9)
R-licarbazepine (BIA 2-195)	400 mg (n=7)	811 (223)	6.0 (6.0-12.0)	15650 (5840)	27.9 (13.7)
	800 mg (n=26)	949 (458)	8.0 (1.0-12.0)	18929 (9630)	25.3 (18.2)
	1200 mg (n=18)	1553 (409)	6.0 (2.0-12.0)	32120 (8304)	61.2 (58.7)
OXC	400 mg (n=7)	168 (67.6)	3.0 (1.0-6.0)	1935 (1271)	11.5 (1.9)
	800 mg (n=26)	232 (84.7)	3.0 (1.0-12.0)	2921 (1103)	12.0 (5.0)
	1200 mg (n=18)	385 (151)	3.0 (1.0-6.0)	5076 (1691)	14.3 (5.8)

Following oral administration of SEP-0002093 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 $t_{1/2}$ of 12.8 h, 13.5 h, and 20.2 h, respectively. The variability in the patient population seemed higher, probably due to the concomitant AEDs.

2.2.12 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

(RS)-licarbazepine:

In healthy subjects:

- After single dose, plasma concentrations of (RS)-licarbazepine increased with increasing doses of SEP-0002093 (Study 101). The increase in systemic exposure to (RS)-licarbazepine was approximately dose proportional. The extent of the deviation from dose proportionality for C_{max} and $AUC_{0-\tau}$ based on Study 101 is:
    - The extent of systemic exposure or (RS)-licarbazepine, assessed by C_{max}, increased in a statistically significantly less-than-proportional manner for (RS)-licarbazepine. This is given by the exponent of the power function fitted to the individual Cmax data: 0.95 (CI 0.91, 0.99) for C_{max}
    - The extent of systemic exposure, assessed by $AUC_{0-\tau}$, increased in a greater-than-dose-proportional manner. This is given by the exponent of the power function fitted to the individual $AUC_{0-\tau}$ data: 1.17 (CI 1.14, 1.20) for $AUC_{0-\tau}$
- The extent of the deviation from dose proportionality for C_{max} and $AUC_{0-\tau}$ based on Study 102 is:

- The exponent of the power function fitted to the individual Cmax data was 0.6 (CI 0.46, 0.82)
- The exponent of the power function fitted to the individual AUC0-t data was 0.9 (CI 0.70, 1.03)

- The mean apparent terminal half-life of (RS)-licarbazepine ranged from 8 to 17 h (tending to increase with dose).
- Renal clearance of (RS)-licarbazepine was approximately 20 mL/min, irrespective of the dose administered.
- The amount of (RS)-licarbazepine recovered in the urine increased with increasing dose level, consistent with the greater-than-dose-proportional increase in extent of systemic exposure in plasma.
- Since, renal clearance of (RS)-licarbazepine appeared to be constant over the dose range studied, indicating that the dose-dependent, fractional increase in urinary recovery was due either to increased formation of (RS)-licarbazepine with increasing dose level or decreased non-renal elimination of the metabolite.

The relationship between AUC0-24h and Cmax values of BIA 2-005 and dose of BIA 2-093 following a single oral administration is given in the the following Figures:

Figures: Relationship between AUC0-24h and Cmax Values of BIA 2-005 and Dose (day 1)

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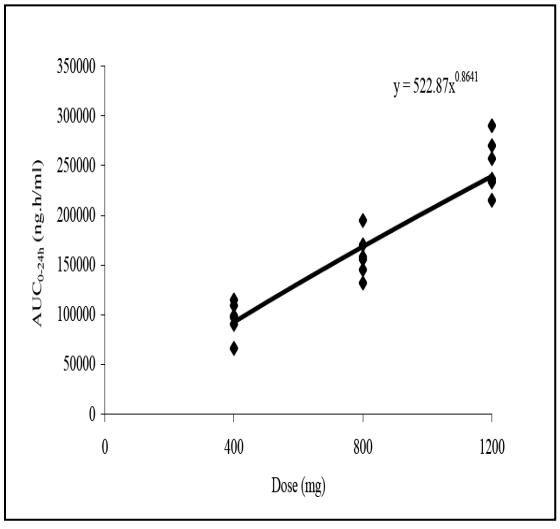

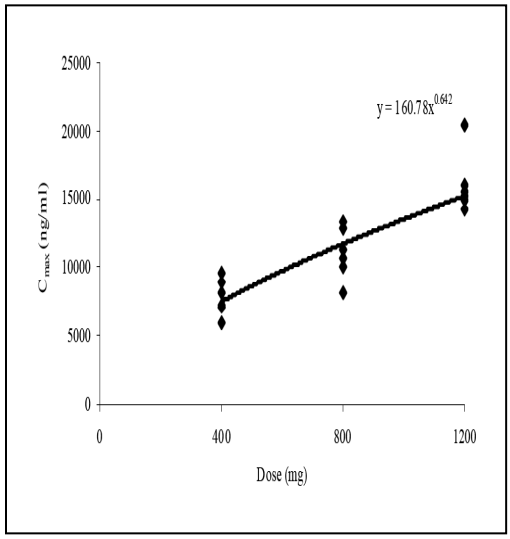

After multiple doses, plasma concentrations of (RS)-licarbazepine increased in an approximate dose proportional manner:

- The exponent of the power function fitted to the individual Cmax data was 1.0 (CI 0.83, 1.30)

- The exponent of the power function fitted to the individual AUC0-t data was 1.1 (CI 0.98, 1.22)

The following Figure displays the ratios between mean (RS)-licarbazepine AUC_{0-24} and SEP-0002093 dose in the dose range 400-2400 mg QD, and between mean (RS)-licarbazepine C_{max} and SEP-0002093 dose in the dose range 400-2400 mg QD, when multiple dose data is combined from Study 113

Figure: Ratios Between (RS)-licarbazepine AUC0-24 (ng·h/mL) and SEP-0002093 Dose (mg) and Between Cmax (ng /mL) and SEP-0002093 Dose (mg) After Administration of the Last Dose of an 8-Day Repeated Dose Regimen of SEP-0002093 200 mg BID and 400 to 2400 mg QD

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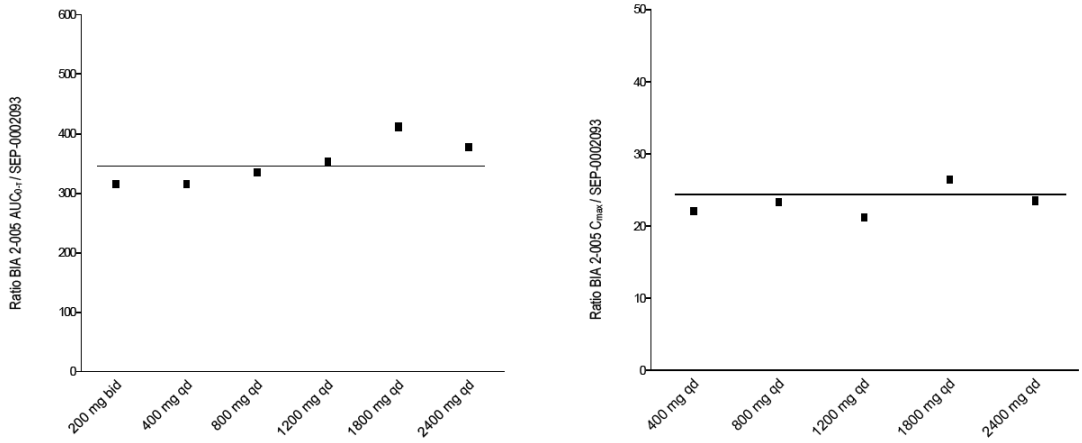
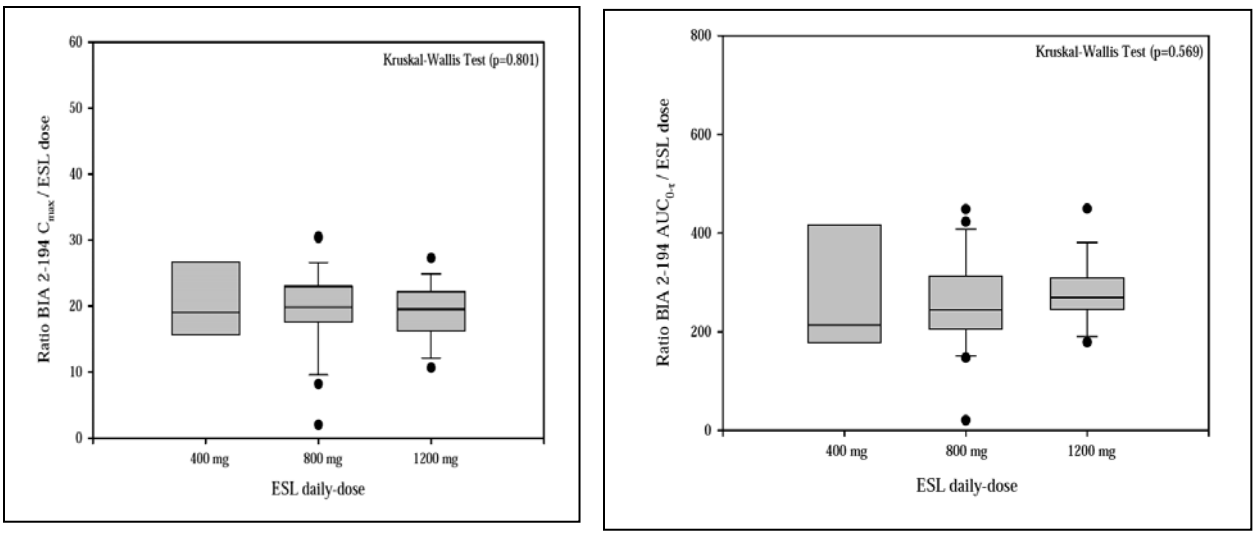


Eslicarbazepine:

In patients:

Dose proportionality was assessed in a subset of patient (N=51) from the Phase III study (Study 301) with intense plasma sampling as shown in the following Figures for Cmax and AUC
These figures suggest approximate dose proportionality for Cmax and AUC of eslicarbazepine.

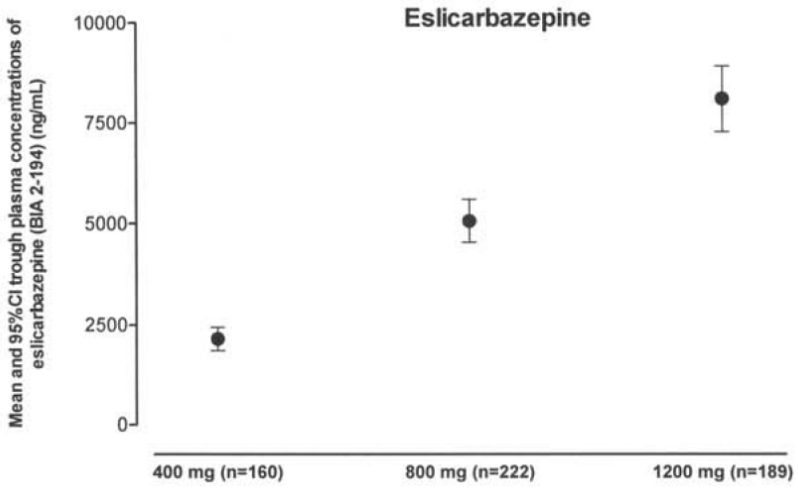
Figure: Box-plot of eslicarbazepine (BIA 2-194) Cmax/ESL and AUC0-24/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



In addition to this, trough plasma samples for the assay of eslicarbazepine were also collected at the end of the 12-week treatment of the three pivotal Phase III studies (Study 301, 302, 303) in 1050 patients. Blood sampling was performed before next dose. Mean (and respective 95% CI) of eslicarbazepine "trough" concentrations following administration of ESL 400 mg, 800 mg and 1200 mg were calculated. A total of 160 patients (400 mg ESL group), 222 (800 mg group), and 189 (1200 mg group) were included in the analysis in a total of 571 "trough" eslicarbazepine plasma concentrations.

	ESL 400mg	ESL 800 mg	ESL 1200 mg
Mean (ng/mL)	2148	5060	8089
95%CI	1856;2440	4526;5593	7267;8912

This also suggested dose proportionality in plasma trough concentration in patients on doses ranging from 400-1200 mg.



Oxcarbazepine:

The values of the exponent of the power function for AUC0-24h and Cmax was 1.17 (CI, 0.95, 1.40) and 1.2 (CI, 0.94, 1.45), respectively, indicating that the extent of systemic exposure tended to increase in an approximately dose proportional manner over the dose range of 400 to 1200 mg.

2.2.13 How does QD dosing of Eslicarbazepine Acetate compare to BID dosing?

QD and BID dosing of 900 mg was assessed in Study 110. The sponsor is only proposing QD dosing in the current application. The extent of exposure to active

moieties, eslicarbazepine, R-licarbazepine and oxcarbazepine (as assessed by AUC) during 24 hours while on a BIA 2-093 900 mg once-daily regimen was identical to that induced by a BIA 2-093 450 mg twice daily regimen (ratio BIA 2-093 900 mg / BIA 2-093 450 mg AUC_{0-24} / 2xAUC_{0-12} = 1.03 for eslicarbazepine), as shown in the following Table:

Table: Ratio between the eslicarbazepine (BIA 2-194), R-licarbazepine (BIA 2-195) and oxcarbazepine (OXC) AUC0-τ (AUC0-24h)

	OXC	BIA 2-194	BIA 2-195	Sum
BIA 2-093 900 mg od (A)	3030 ng.h/mL (0.99%)	288280 ng.h/mL (94.64%)	13299 ng.h/mL (4.37%)	304609 ng.h/mL (100%)
BIA 2-093 450 mg bid (B)	3230 ng.h/mL (1.08%)	280002 ng.h/mL (94.00%)	14638 ng.h/mL (4.92%)	297870 ng.h/mL (100%)
Ratio A/B	0.94	1.03	0.91	1.02

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 Effect of Renal Impairment:

Dose reductions are recommended in the patients with moderate and severe renal impairment.

The extent of systemic exposure (AUC0-∞) to BIA 2-194 increased by 62% in the mild renal impairment group, 116% (2-fold) in the moderate renal impairment group and 154% (2.5 fold) in the severe renal impairment group in comparison to the healthy subjects following a 800 mg single dose as shown in the Table below. However, the relative proportion of active moieties remained reasonably similar in the different groups, with eslicarbazepine corresponding to approximately 92%-94% of systemic exposure.

Table: Comparison of Mean Pharmacokinetic Parameters of SEP-0002093 (800 mg) Metabolites in Subjects with Mild, Moderate, and Severe Renal Impairment in Relation to Matched Healthy Subjects (n=8 per group)

Parameter	Mild / Control Ratio (95% CI)	Moderate / Control Ratio (95% CI)	Severe / Control Ratio (95% CI)
Eslicarbazepine			
C_{max} (ng/mL)	1.31 (1.06; 1.62)	1.05 (0.85; 1.30)	1.05 (0. 85; 1.30)
$AUC_{0-\infty}$ (ng·h/mL)	1.61 (1.18; 2.20)	2.11 (1.55; 2.88)	2.54 (1.86; 3.46)
$t_{½}$ (h)	0.99 (0.72; 1.37)	1.67 (1.21; 2.30)	2.64 (1.91; 3.65)
CL_R (mL/h)	0.59 (0.42; 0.84)	0.21 (0.15; 0.30)	0.09 (0.06; 0.13)
t_{max} (h)	p = 0.4987	p = 0.0198	p = 0.0315
Eslicarbazepine-GLU			
C_{max} (ng/mL)	0.52 (0.31; 0.88)	1.80 (1.06; 3.05)	1.78 (1.05; 3.01)
$AUC_{0-\infty}$ (ng·h/mL)	1.33 (0.80; 2.19)	5.84 (3.75; 9.11)	11.59 (7.32; 18.34)
$t_{½}$ (h)	1.05 (0.63; 1.77)	2.52 (1.59; 3.98)	4.44 (2.76; 7.13)
CL_R (mL/h)	0.85 (0.44; 1.63)	0.20 (0.11; 0.36)	0.08 (0.04; 0.14)
t_{max} (h)	p = 0.3297	p = 0.1867	p = 0.0085
(R)-licarbazepine			
C_{max} (ng/mL)	1.65 (1.25; 2.19)	1.95 (1.47; 2.58)	2.21 (1.66; 2.93)
$AUC_{0-\infty}$ (ng·h/mL)	1.36 (0.66; 2.80)	1.96 (0.96; 3.98)	3.11 (1.53; 6.32)
$t_{½}$ (h)	0.74 (0.36; 1.54)	0.75 (0.36; 1.53)	1.18 (0.57; 2.42)
CL_R (mL/h)	1.03 (0.50; 2.31)	0.42 (0.20; 0.90)	0.17 (0.08; 0.36)
t_{max} (h)	p = 1.0000	p = 0.2207	p = 0.0218
(R)-licarbazepine-GLU			
C_{max} (ng/mL)	1.54 (0.91; 2.62)	2.82 (1.66; 4.80)	5.31 (3.13; 9.02)
$AUC_{0-\infty}$ (ng·h/mL)	6.25 (1.69; 23.07)	20.61 (5.59; 76.06)	103.52 (21.74; 492.82)
$t_{½}$ (h)	3.93 (1.03; 14.97)	5.77 (1.51; 21.99)	14.85 (3.00; 73.46)
CL_R (mL/h)	0.18 (0.05; 0.59)	0.05 (0.02; 0.18)	0.01 (0.00; 0.04)
t_{max} (h)	p = 0.6007	p = 0.0060	p = 0.0044

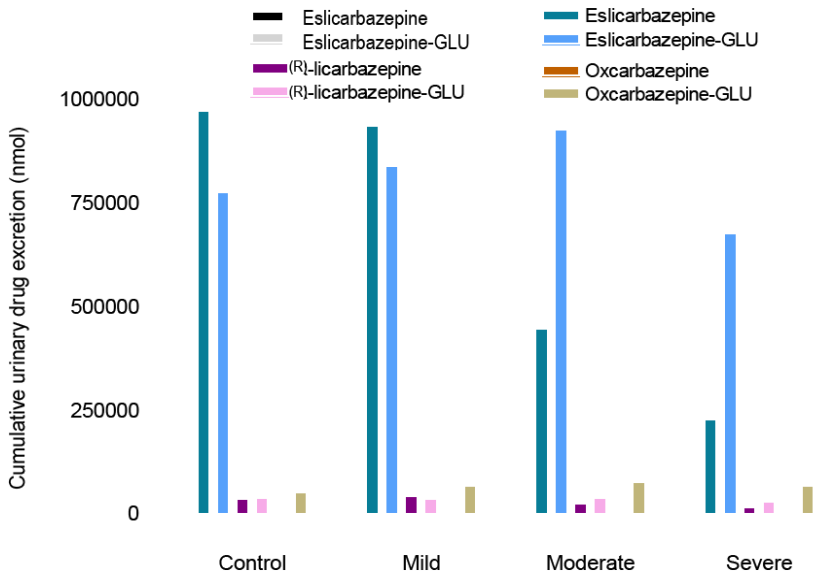
Eslicarbazepine t_{max} occurred at 1 h post-dose in the normal and mild renal impairment groups, and increased to approximately 3 h in the moderate and severe renal impairment groups. Apparent $t_{1/2}$ was similar between the normal and mild renal impairment groups (approximately 11 h), but was significantly increased to 18 h and 28 h in the moderate and severe renal impairment groups, respectively.

The total amount of eslicarbazepine recovered in urine from time of dosing until 72 h post-dose was similar in the control and mild renal impairment groups, but a marked

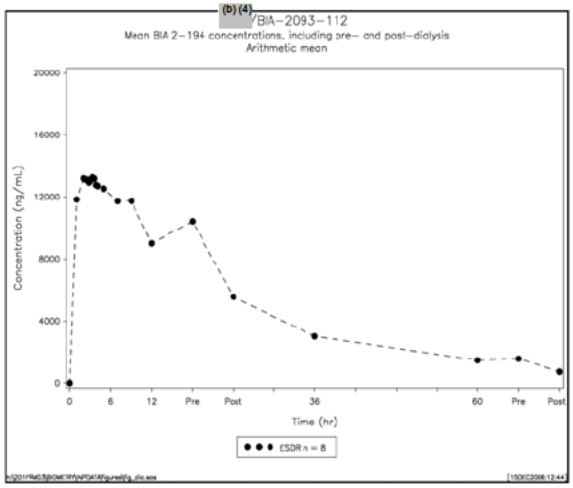
decrease was found in the moderate and severe renal impairment groups (see following Figure).

The pharmacokinetics of the minor metabolites (eslicarbazepine-GLU, (R)-licarbazepine, and (R)-licarbazepine-GLU) were significantly affected by renal function. Systemic exposure to each metabolite was increased with the degree of the renal impairment, as consequence of longer half-lives and lower total body clearance and renal clearance. In the control group, eslicarbazepine corresponded to approximately 52% and eslicarbazepine-GLU to 41% of total amount of drug recovered in urine; the mild renal impairment group showed similar proportions (49% versus 44%, respectively), but a marked change was found in the moderate and severe renal impairment groups (29% versus 61% and 22% versus 66%, respectively).

Figure: Mean Cumulative Urinary Excretion (in nmol) of SEP-0002093 and its Metabolites in Urine Collected from 0 to 72 h Post-Dose (n=8 per group)



Repeated hemodialysis was effective in removing the SEP-0002093 metabolites from the systemic circulation as shown in the figure below:



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Impact of CrCL based on population analysis:

In the population analysis of three phase III studies, the renal function which was evaluated by Creatinine Clearance (CrCL) was not found to be significant factor on eslicarbazepine PK. The sponsor provided two potential reasons for that. One possibility is that the incorporation of the effect of weight on CL/F using the allometric function is serving as a surrogate for the effect of renal function as the Cockcroft and Gault-predicted CrCL values are correlated with weight. Another possibility is that the number of patients with CrCL values low enough to impact eslicarbazepine CL/F values observed in these studies was not large enough to detect a statistically significant effect on CL/F (7% of patients had CrCL values < 80 mL/min and 1% had CrCL < 50 mL/min).

Dosage adjustment:

Sponsor proposed:

The sponsor proposed initial dosing to be (b) (4) The sponsor's proposal is given in the following Table:

(b) (4)

The simulations to show sponsor's proposal are in the following Figure:

(b) (4)

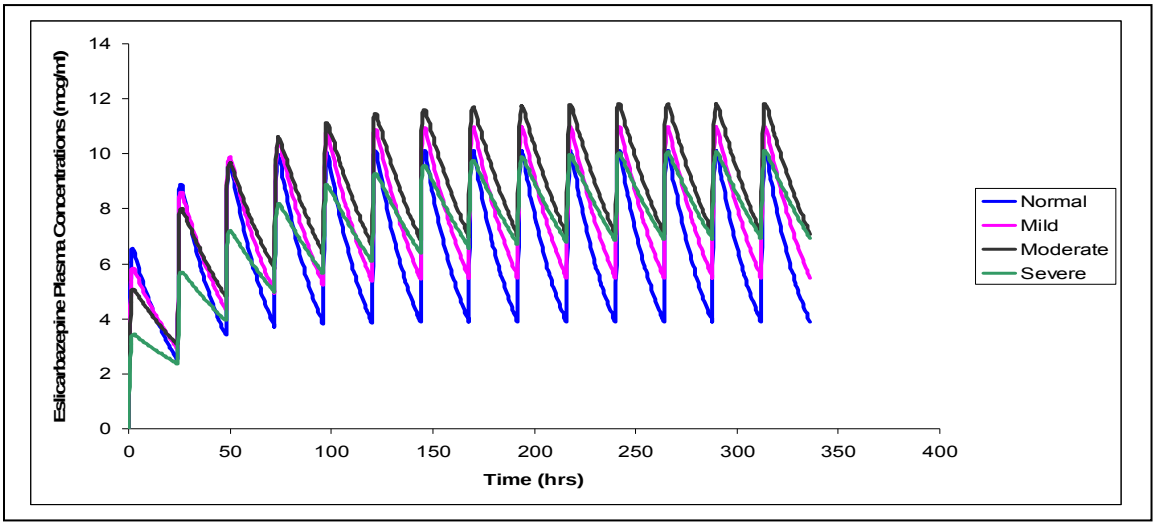
Reviewer Proposed:

Dosing Recommendations	Normal	Mild	Moderate	Severe
Initial	400 mg QD for 1 week	400 mg QD for 1 week	300 mg QD for 1 week	200 mg QD for 1 week
Maximum	1200 mg QD	1200 mg QD	600 mg QD	600 mg QD

(b) (4)

The simulated profiles for the titration and maintencance phases based on reviewer's recommendations are given in the following Figure:

Figure: Plasma concentration profile in the first two weeks of titration phase based on reviewer recommended doses:



(b) (4)

This can be considered, because the lowest strength available is 400 mg. The 600 and 800 mg tablets are scored on one side and can be split, however, the 400 mg tablets is a small round tablets, the splitting of which may not be feasible. Another consideration could be to develop a lower strength in the future.

Simulations for the plasma concentrations at the maintenance dose are given in the following Figure:

Figure: Plasma concentration profile at steady state at the sponsor and reviewer recommended doses:

(b) (4)

The sponsor was requested to clarify and provide rationale for their dosing recomemdations for the renally impaired patients. In their response, the sponsor also agreed and recommeded a maximum of 600 mg in the moderate and severe impaired groups.

The predicted steady sate Cmax and AUC after a 600 mg dose is given in the following Table, which supports the use of this dose.

Table: Steady-State PK Parameters in Renal Impairment Subjects (Simulation) and In Epileptic Patients (Observed data from PK Sub-Study)

	Epileptic Patients	Moderate	Severe
	1200 mg QD	**600 mg QD**	**600 mg QD**
Mean C_{max} (ng/mL) (Range)	22957 (12770, 32753)	19323	24250
Mean $AUC_{0\text{-}tau}$ (ng*h/mL) (Range)	336147 (214866, 539385)	352125	465070

2.3.1. 2 Effect of Hepatic Impairment:

The pharmacokinetics of eslicarbazepine in subjects with moderate hepatic impairment was not different from the healthy subjects.

Effect of hepatic impairment was evaluated only in subjects with moderate impairment (7-9 points on the Child-Pugh assessment) compared to healthy subjects after multiple doses of 800 mg QD for 8 days as eslicarbazepine is mainly eliminated renally either unchanged or as glucuronides.

The pharmacokinetic parameters in the hepatic impaired subjects compared to healthy subjects are shown in the following Table:

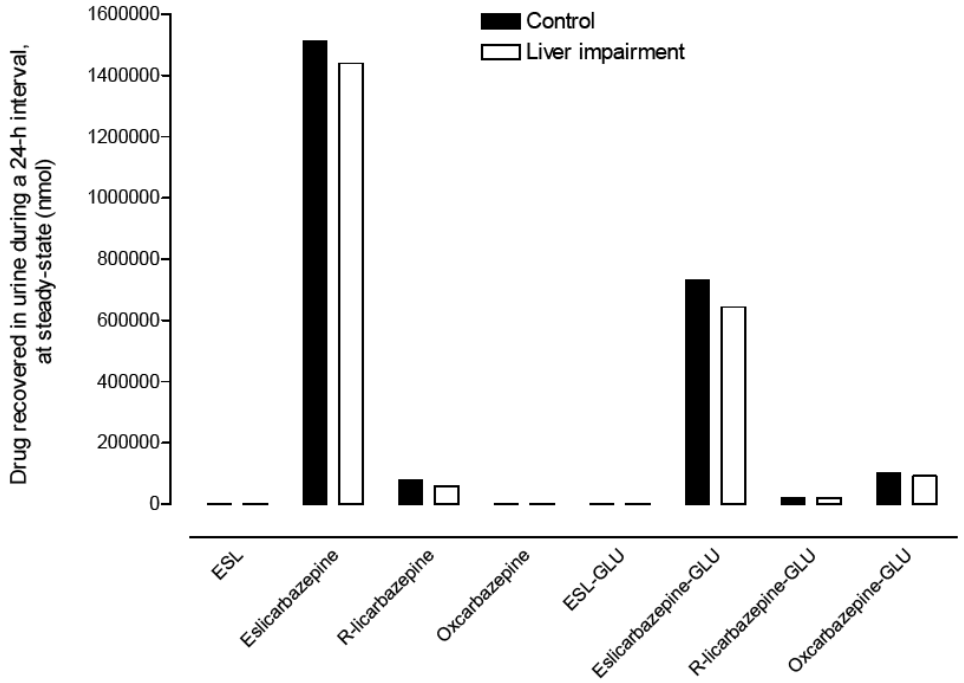
Table: Geometric Mean Pharmacokinetic Parameters and Statistical Analysis of SEP-0002093 Metabolites, Including Glucuronides (GLU), Following the Last Dose (Day 8) of 800 mg QD Oral Administration to a Group of Moderately Liver Impaired and Matched Healthy Subjects

Analyte Parameter	Healthy Control Group		Moderate Liver Impairment Group		Ratio Impaired / Control (95% CI)
	N	Mean	N	Mean	
Eslicarbazepine					
C_{max} (ng/mL)	8	27,219	8	25,773	0.95 [0.76 ; 1.18]
t_{max} (h)	8	1.0	8	1.8	p = 0.86
$AUC_{0\text{-}24}$ (ng·h/mL)	8	368,958	8	372,854	1.01 [0.79 ; 1.30]
$t_{½}$ (h)	8	10.9	8	12.9	1.19 [0.79 ; 1.80]
CL_R (mL/h)	8	1,388	8	1,334	0.96 [0.71 ; 1.30]
(R)-licarbazepine					
C_{max} (ng/mL)	8	924	8	787	0.85 [0.60 ; 1.22]
t_{max} (h)	8	9.5	8	8.0	p = 0.87
$AUC_{0\text{-}24}$ (ng·h/mL)	8	19,907	8	17,028	0.86 [0.59 ; 1.24]

$t_{½}$ (h)	8	18.3	8	17.4	0.95 [0.72 ; 1.26]
CL_R (mL/h)	8	1,592	8	1,426	0.90 [0.65 ; 1.24]
Eslicarbazepine-GLU					
C_{max} (ng/mL)	8	1,007	8	1,370	1.36 [0.62 ; 2.99]
t_{max} (h)	8	4.6	8	7.0	P=0.96
AUC_{0-24} (ng·h/mL)	8	5,701	8	8,734	1.53 [0.54 ; 4.33]
$t_{½}$ (h)	8	18.7	8	16.0	0.85 [0.47 ; 1.54]
CL_R (mL/h)	8	67,685	8	33,204	0.49 [0.17 ; 1.44]
(R)-licarbazepine-GLU					
C_{max} (ng/mL)	8	74	8	43	0.58 [0.25 ; 1.38]
t_{max} (h)	8	6.0	8	9	P=0.46
AUC_{0-24} (ng·h/mL)	8	566	8	324	0.57 [0.17 ; 1.91]
$t_{½}$ (h)	8	14.5	8	23.2	1.61 [1.00 ; 2.57]
CL_R (mL/h)	8	28,585	8	31,958	1.12 [0.33 ; 3.78]

The urinary excretion in the healthy and hepatic impaired group is given in the Figure below:

Figure: Mean Cumulative Urinary Excretion (in nmol) of SEP-0002093 and its Metabolites in Urine Collected During a 24-Hour Interval on Day 8 (n=8 per group)



- In the hepatic impaired group, inhibition of the hepatic metabolism of the parent drug, **eslicarbazepine acetate or SEP-0002093 or BIA 2-093**, in the group with hepatic impairment was evident. In the hepatic impairment group, there were notably more subjects with measurable BIA 2-093 plasma concentrations, but systemic exposure to BIA 2-093 was about 0.01% of systemic exposure to BIA 2-194 and, therefore, it is not expected that BIA 2-093 will have a significant contribution to the therapeutic effects.
- For **Eslicarbazepine or BIA 2-194**, no statistically significant difference was found between the hepatic impaired group and the healthy control group. Mean ratios (impaired/control) for Cmax and the AUC variables of BIA 2-194 ranged between 95% and 101% on Day 8. A trend toward higher concentrations of **BIA 2-194 glucuronide** was found in moderate liver impairment group. Extent of systemic exposure to BIA 2-194 glucuronide corresponded approximately to 2%-3% of exposure to BIA 2-194, in both groups. Urine excretion of BIA 2-194 and BIA 2-194 glucuronide was similar between liver impaired and healthy subjects, and the amount of BIA 2-194 recovered in urine in the unchanged form was approximately 2-fold higher than the amount recovered in the glucuronide form.
- For **R-licarbazepine or BIA 2-195**, no statistically significant difference was found between the hepatic impaired group and the healthy control group regarding the rate and extent of its formation. The mean ratios (impaired/control) for Cmax and the AUC variables for BIA 2-195 ranged between 85% and 86% on Day 8. A trend towards decreased exposure was observed for **BIA 2-195 glucuronide.** Extent of systemic exposure to BIA 2-195 glucuronide was approximately 3% of exposure to BIA 2-195, in both groups. Urine excretion of BIA 2- 195 and BIA 2-195 glucuronide was similar between liver impaired and healthy subjects, and the amount of BIA 2-195 recovered in urine in the unchanged form was approximately 3-fold or 4-fold lower than the amount recovered in the glucuronide form.
- For **oxcarbazepine**, the results indicate that no statistically significant difference between the hepatic impaired group and the healthy control group regarding the rate and extent of its formation. On Day 8, the mean ratios (impaired/control) for Cmax, ss and AUCss for oxcarbazepine were 84% and 94%, respectively. Urine excretion of oxcarbazepine and oxcarbazepine glucuronide was similar in liver impaired and healthy subjects, and the amount of oxcarbazepine recovered in urine in the unchanged form was much lower (~ 2%) than the amount recovered in the glucuronide form.

Dosage adjustment:
No dosage adjustment is necessary in adults with mild and moderate hepatic impairment. A study in severe impaired patients has not been conducted.

2.3.1.3 Effect of age:

Elderly:
The pharmacokinetic in the elderly that had creatinine clearance ≥ 67 mL/min were

similar to the young subjects.

The pharmacokinetic differences in the elderly (65 yearsor older) and young (18-40 years) healthy subjects were assessed after single (600 mg) and multiple doses (600 mg QD for 8 days).

The geometric mean pharmacokinetic parameters of eslicarbazepine and (R)-licarbazepine in the elderly and young subjects are shown in the following Table:

Table: Geometric Mean Pharmacokinetic Parameters of Eslicarbazepine and (R)-licarbazepine Following Single- and Multiple-Dose Administration of SEP-0002093 600 mg to Elderly and Young Subjects

Analyte Parameter		Elderly Group (≥ 65 years)	Young Group (18-40 years)	Ratio (Elderly/ Young)	95% CI	p-value
Eslicarbazepine						
C_{max} (ng/mL)	Single-dose Multiple-dose	9,332 14,942	9,743 16,990	0.948 0.879	0.81;1.14 0.77;1.03	0.504 (NS) 0.0781 (NS)
t_{max} (h)	Single-dose Multiple-dose	3.00 2.00	2.50 1.5	-0.0417* 0.000*	-1.68;1.60 -1.07;1.07	0.930 (NS) 0.434 (NS)
$AUC_{0-\infty}$ (ng·h/mL)	Single-dose Multiple-dose	187,793 291723	177,298 289233	1.06 1.01	0.88;1.32 0.89;1.18	0.586 (NS) 0.914 (NS)
(R)-licarbazepine						
C_{max} (ng/mL)	Single-dose Multiple-dose	200 506	190 443	-	-	-
t_{max} (h)	Single-dose Multiple-dose	12.0 8.00	10.0 8.00	-	-	-
$AUC_{0-\infty}$ (ng·h/mL)	Single-dose Multiple-dose	- 20,996	- 17,944	-	-	-

C_{max}, AUC_{τ}, and $AUC_{0-\infty}$ expressed as geometric mean; t_{max} expressed as median
*Difference (Elderly-Young). 95%CI = 95% Confidence Interval, NS = Not significant

After a 600-mg single dose, mean C_{max} and $AUC_{0-\infty}$ of eslicarbazepine were not significantly different in the young and elderly groups, indicating that age did not increase exposure to eslicarbazepine. Eslicarbazepine $t_{1/2}$ was 10.1 h and 10.9 h in the young and elderly groups, respectively.

Following 600 mg QD for 8 days, steady-state eslicarbazepine plasma concentrations were attained after 4 to 5 days of administration in both age groups. Eslicarbazepine was shown to be the major metabolite, representing approximately 95% and 96% of total systemic drug exposure (as assessed by AUC_{0-24}) in elderly and young subjects, respectively. In the young and elderly groups, an observed accumulation factor (R_0) of 1.64 and 1.59, respectively, was estimated. Following the last dose, mean C_{max} and

$AUC_{0-\infty}$ were not significantly different in the young and elderly groups, indicating that age did not increase exposure to eslicarbazepine. Eslicarbazepine $t_{1/2}$ was 10.5 h and 11.1 h in the young and elderly groups, respectively.

In conclusion, the pharmacokinetic profile of eslicarbazepine was similar in young and elderly subjects.

Dosage adjustment:
No dosage adjustment is necessary in adults based on age, if their creatinine clearance is ≥ 50 ml/min.

2.3.1.4 Effect of Gender:

There was no gender difference in the pharmacokinetics of eslicarbazepine.

The pharmacokinetic differences in the male and female healthy subjects were assessed after single (600 mg) and multiple doses (600 mg QD for 8 days).

The geometric mean pharmacokinetic parameters of eslicarbazepine and (R)-licarbazepine are shown in the following Table:

Table: Geometric Mean Pharmacokinetic Parameters of Eslicarbazepine and (R)-licarbazepine Following Single- and Multiple-Dose Administration of SEP-0002093 600 mg to Males and Females

		Female	Male	Ratio (Female/Male)	95%CI	*p-value*
C_{max}	Single-dose	9879	9104	1.09	0.871;1.43	0.331 (NS)
	Multiple-dose	16727	15177	1.10	0.979;1.27	0.219 (NS)
t_{max}	Single-dose	3.00	2.00	0.625*	-0.744;1.99	0.153 (NS)
	Multiple-dose	2.00	1.30	0.667*	-0.453;1.79	0.0852 (NS)
$AUC_{0-\tau}$	Single-dose	146545	126732	1.16	0.948;1.48.	0.0922 (NS)
	Multiple-dose	249920	204148	1.04	0.881;1.28	0.546 (NS)
$AUC_{0-\infty}$	Single-dose	197212	168830	1.17	0.902;1.63	0.127 (NS)
	Multiple-dose	291975	288983	1.01	0.829;1.30	0.910 (NS)

C_{max}, $AUC_{0-\tau}$ and $AUC_{0-\infty}$ expressed as geometric mean (ng/mL); t_{max} expressed as median (h).
*Difference (Female-Male).
95%CI = 95% Confidence Interval.
NS = Not significant.

The geometric mean ratios for Cmax and AUC were within 1.01-1.17 after single and multiple doses. This indicates that there are no significant difference in the pharmacokinetic parameters between males and females. There were no differences when analyzed separately for the elderly or the young group either.
Gender was not a significant covariate in the population analysis as well.

Dosage adjustment:
No dosage adjustment is necessary based on gender.

2.3.1.5 Effect of Race:

The sponsor evaluated race effect as black .vs. non-black population where non-black population included Caucasian, Asian and Hispanic and the sponsor claimed that race did not influence on eslicarbazepine CL/F. However, the reviewer's analysis showed that the number of Asian patients was too small for comparisons with sufficient power, as shown in the Table below. However, no pharmacokinetic differences were observed between the Caucasians, Blacks and Hispanics.

Table. The distribution of Race in population PK analysis dataset.

Race/Ethnicity	BIA 2093-301 (N=311)	BIA 2093-302 (N=207)	BIA 2093-303 (N=111)	Overall (N=629)
Caucasian	311	183	40	534
Black	0	12	0	12
Asian	0	5	1	6
Hispanic	0	7	70	77

Dosage adjustment:
No dosage adjustment is necessary between Caucasians, Blacks and Hispanic.

2.4 EXTRINSIC FACTORS

2.4.1 Is eslicarbazepine acetate a substrate, inhibitor or inducer of CYP enzymes?

Substrate: Eslicarbazepine acetate is not a substrate of any CYP isoenzymes. It undergoes hydrolytic first pass metabolism by hydrolases.

Inhibitor: 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, or CYP3A4 and only a moderate inhibitory effect on CYP2C9 (20% reduction at 50 μg/ml and 38% reduction at 100 μg/ml) and CYP2C19 (20% reduction at 30 μg/ml and 31% reduction at 100 μg/ml). A mild activation of UGT1A1-mediated glucuronidation (39% increase) was observed *in vitro* in human hepatic microsomes. The inhibition potential of eslicarbazepine for CYP2C8 has not been evaluated. Inhibitory potential of oxcarbazepine and R-licarbazepine have not been

evaluated. Since the overall exposure of these are <1 and 4% respectively, these will not be requested as Phase 4 requirements. It should be noted that the approved Trileptal® label states that it inhibits 2C19, but was not found to be an inhibitor of CYP2C9, as observed with eslicarbazpeine. An in vivo drug interaction study with warfarin and eslicarbazepine did not show an inhibition effect of S-warfarin. Trileptal® also inhibits CYP3A4, but at high concentrations.

Inducer: The active moieties, Eslicarbazepine, R-licarbazepine and oxcarabazepine are not considered to be an inducer of CYP3A4 and Eslicarbazepine is not considered an inducer of Phase II enzymes involved with glucuronidation and sulphation of 7-hydroxy-coumarin in human hepatocytes *in vitro*. The induction of CYP1A2, has not been adequately evaluated, as the positive controls do not show the same magnitude of induction of CYP1A2 as expected, 14-24 fold for omeprazole and 6-26 fold for 2-MC, although the inducer concentrations were adequate in the test system. Since Trileptal® is not an inducer of CYP1A2, a repeat of this is not necessary. It should be noted that the Trileptal® label states that it induces 3A4. Sponsor repeated the experiment and did not find eslicarbazepine to be an inducer of 3A4. Although, an in vivo drug interaction study with oral contraceptives showed that the levels of ethinyl estradiol and levonorgestrel was reduced when co administered with eslicarbazepine. Therefore, the sponsor's in vitro results do not seen reliable.

2.4.2 Is Eslicarbarbazepine a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

This has not been evaluated. However a drug interaction study was conducted with Digoxin. The Cmax and AUC ratios for digoxin were 0.85 and 0.96, suggesting eslicarbazepine is unlikely to be an inhibitor of PgP. An drug interaction study with cyclosporine and verapamil showed a reduction the mono hydroxyl derivative of Trileptal®, suggesting eslicarbazepine is unlikely a substate of P-gp.

2.4.3 Is there an in vitro basis to suspect drug-drug interaction?

Eslicarbazepine inhibits CYP 2C9 and 2C19; therefore, drugs that are substrates of these CYP enzymes could have an increase in exposure. IC50 or Ki determination for the inhibition of CYP2C9 was not conducted; however, the sponsor conducted an *in vivo* drug interaction study with phenytoin (2C9 and 2C19 substrate) and warfarin (2C9 and 2C19 substrate). The results of these studies showed that the Phenytoin levels increased by 31%, possibly due to the inhibition of CYP2C9 or CYP2C19. S-warfarin levels were decreased by 23%, which is inconsistent with the inhibitory effect observed. *In vitro* studies did not show that eslicarbazepine is an inducer of CY3A4, although a decrease in plasma levels of ethinyl estradiol by 33% and levonorgestral by 26% was observed.

Induction of Phase II enzymes involved in glucuronidation and sulphation of 7-hydroxy coumarin was not observed.

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of extrinsic factors like herbal products and smoking have not been conducted. Eslicarbazepine acetate is not metabolized by any of the CYP enzymes.

2.4.5 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.5.1 Influence of eslicarbazepine on other drugs:

Influence of Eslicarbazepine on the pharmacokinetics of concomitant drugs is summarized in the following Table:

Concomitant Medication	Concomitant medication dose	Eslicarbazepine acetate doses evaluated	Cmax Ratio (90% CI) w/wo ESI % Change	AUC Ratio (90% CI) w/wo ESI % Change	Dosage Adjustment
Digoxin (Lanoxin®)	LD: 0.5 mg on days 1-2, then, 0.25 mg days 3-8	1200 mg daily for 8 days	0.85 (0.68;1.07)* 15%↓	0.96 (0.90;1.03) 4%↓	None
Warfarin	5 mg on days 1 -3, then, dose to maintain INR 1.3- 1.8 for 7 day	1200 mg daily for 7 days	S-Warfarin 0.81 (0.76;0.86)* 19%↓ R-Warfarin 0.97 (0.91;1.02) 3%↓	S-Warfarin 0.77 (0.72;0.82)* 23%↓ R-Warfarin 0.98 (0.92;1.04) 2%↓	Patients should be monitored to maintain INR
Oral Contraceptive: Microginon® (ehtinylestradiol and levonorgestrel)	30 µg ethinylestradiol + 150 µg levonorgestrel (OC) on day 1 of OC period and day 14 of	1200 mg daily on days 1 – 15 of OC + ESI period	Ethinylestradiol 0.80 (0.71;0.92)* 20%↓ Levonorgestrel 0.87 (0.79;0.95)*	Ethinylestradiol 0.58 (0.55;0.62)* 42%↓ Levonorgestrel 0.63 (0.55;0.72)*	Additional or alternative non-hormonal birth control should be

	OC + ESI period		13%↓	37%↓	used
Metformin	850 mg Day 5	1200 mg Day 1-5	Metformin 0.88 (0.77; 1.00) 12% ↓	Metformin 0.95 (0.85; 1.06) 5% ↓	No

The influence of these other drugs in eslicarbazepine exposure has not been evaluated.

2.4.5.2 Influence of eslicarbazipine acetate on concomitant AEDs

The influence of eslicarbazepine on AEDs is shown in the following Table:

Concomitant AED	Concomitant AED dose	Eslicarbazepine doses evaluated	Cmax Ratio (90% CI) w/wo eslicarbazepine % change	AUC Ratio (90% CI) w/wo eslicarbazepine	Dosage Adjustment of AED
Lamotrigine	150 mg daily for 6 days	1200 mg once daily for 6 days	0.88 (81.74;94.30) 12%↓	0.86 (80.62; 91.80) 14%↓	No
Topiramate	200 mg once daily for 17 days	1200 mg daily for 17 days	0.82 (77.48;85.89)* 18%↓	0.82 (79.69;84.00)* 18%↓	No
Phenytoin*	300 mg daily for 17 days	1200 mg daily for 17 days	1.31 (116.98;146.11)* 31%↑	1.35 (120.95;151.00)* 35%↑	Yes Decrease phenytoin dose

*Based on population PK analysis; phenytoin CL/F was found to be decreased with increasing eslicarbazepine acetate dose by 3.6%, 7.1%, and 10.7% for eslicarbazepine acetate doses of 400 mg, 800 mg, 1200 mg daily, respectively, as compared to those not receiving concomitant eslicarbazepine acetate. Sponsor's population PK analysis clearly underestimates the effect compared to the results from the dedicated drug interaction as shown in the Table above.

Effect of eslicarbazepine on other AEDs that were evaluated using a population approach only; the results of which are summarized in the following Table:

AED	Dose of AED (mg/day)	Eslicarbazepine acetate Dose (mg/day)	Influence of Eslicarbazepine acetate on AED	Dose Adjustment of AED
Carbamazepine	400-1200	400-1200	4-12% increase on CL/F	No

Phenobarbital	150	1200	No influence	No
Valproate	250-2000	1200	No influence	No
Levetiracetam	750-4000	1200	17% increase in CL/F	No
Gabapentine	800-3600	1200	No influence	No

2.4.5.3 Influence of AEDs on eslicarbazipine acetate:

The influence of concomitant AEDs on eslicarbazepine levels is shown in the following Table

Concomitant AED	Concomitant AED dose	Eslicarbazepine doses evaluated	Cmax Ratio (90% CI) w/wo AED %Change	AUC Ratio (90% CI) w/wo AED %Change	Dosage Adjustment Of Eslicarbazepine acetae
Lamotrigine	150 mg daily for 6 days	1200 mg once daily for 6 days	0.94 (87.49;102.24) 6%↓	0.96 (90.76;101.95) 4%↓	No
Topiramate	200 mg once daily for 17 days	1200 mg daily for 17 days	0.87 (81.06;92.94) 13%↓	0.93 (89.21;96.32) 7%↓	No
Phenytoin*	300 mg daily for 17 days	1200 mg daily for 17 days	0.69 (64.94,70.22) 31%↓	0.67 (64.72;70.22) 33%↓	Yes Higher dose of ESL needed

*No relevant effect of phenytoin on CL/F of eslicarbazepine was observed based on population analysis, where as an in vivo drug interaction study showed a 33% decrease. Thus population analysis underestimates the results for phenytoin.

Effect of other AEDs on eslicarbazepine that were evaluated using a population approach only; the results of which are summarized in the following Table:

AED	Dose of AED (mg/day)	Eslicarbazepine acetate Dose (mg/day)	Influence of AED on Eslicarbazepine acetate	Dose adjustment of eslicarbazepine acetate
Carbamazepine	400-1200	400-1200	11-32% increase on CL/F	Yes A higher dose of eslicarbarzepine may be necessary
Phenobarbital	150	1200	26% increase on CL/F	Yes A higher dose of eslicarbarzepine may

				be necessary
Valproate	250-2000	1200	8-26% decrease on CL/F	No
Levetiracetam	750-4000	1200	No influence	No
Gabapentine	800-3600	1200	No influence	No

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Eslicarbazepine is NOT a BCS I drug product. It has very low aqueous solubility

2.5.2 Is the proposed to-be-marketed formulation of Eslicarbazepine acetate bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The to-be marketed tablet formulation (TBM) of Eslicarbazepine acetate is bioequivalent to the Tablet formulation used in the pivotal clinical trials (CTF: FC formulation) for all the proposed strengths of the Tablet (400, 600 and 800 mg). The BE study was conducted under traditional fasting conditions. Achiral assay as recommended in the Guidance was used in the assessment of bioequivalence. The pharmacokinetic parameters of the *Test* and *Reference* Tablets are shown in the Table below.

Table: Arithmetic Mean (CV%) Pharmacokinetic Parameters of (RS)-licarbazepine Following Oral Administration of a Single Dose of 400 mg, 600 mg, and 800 mg in the Form of Tablet Formulation To-Be-Marketed (TBM) and in the Form of Tablet Formulation Used in Pivotal Clinical Trials (CTF)

	C_{max} (ng/mL)	**t_{max} (h)**	**$AUC_{0-\tau}$ (ng·h/mL)**	**$AUC_{0-\infty}$ (ng·h/mL)**	**$t_{1/2}$ (h)**
400 mg tablet					
TBM (Test)	7,108 (28.2%)	2.0 (44.3%)	125,740 (23.1%)	127,071 (23.5%)	9.4 (28.9)
CTF (Reference)	6,660 (23.2%)	2.5 (49.7%)	122,134 (22.6%)	123,420 (22.9%)	9.3 (28.5%)

600 mg tablet					
TBM (Test)	10,725 (18.1%)	2.5 (48.5%)	219,561 (18.1%)	222,887 (18.4%)	10.4 (23.2%)
CTF (Reference)	10,405 (16.5%)	3.0 (43.3%)	215,750 (20.6%)	219,122 (20.9%)	10.5 (24.7)
800 mg tablet					
TBM (Test)	13,186 (17.5%)	3.0 (54.5%)	294,749 (16.3%)	299,320 (16.5%)	11.1 (17.2)
CTF (Reference)	12,768 (19.8%)	3.0 (43.6%)	293,960 (16.8%)	299,997 (17.1%)	11.1 (19.9%)

The geometric means ratio and 90% confidence interval for the (RS)-licarbazepine pharmacokinetic parameters of interest ($AUC_{0-\infty}$, $AUC_{0-\infty}$, and C_{max}) between *Test* formulations over *Reference* formulation are given in the following Table:

Table: Geometric Means Ratio (GMR) and 90% Confidence Interval for the Comparison of (RS)-licarbazepine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Point Estimate and CI	TBM (Test) / CTF (Reference) GMR and 90% CI		
		400 mg	600 mg	800 mg
C_{max}	GMR (%) 90% CI	105.4 99.6; 111.5	102.7 97.3; 108.3	104.2 95.4; 113.7
AUC_{0-t}	GMR (%) 90% CI	102.8 99.2; 106.6	102.4 99.0; 105.9	100.3 97.9; 102.9
$AUC_{0-\infty}$	GMR (%) 90% CI	102.8 99.1; 106.7	102.4 98.0; 105.9	99.9 97.7; 102.2

In conclusion, the 90% confidence interval of all parameters under consideration (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) fell within the acceptance range of 80 - 125%. Therefore, the formulation to-be marketed and the formulation used in the pivotal clinical trials is considered bioequivalent. The DSI inspection results were acceptable.

2.5.2.1 What data support or do not support a waiver for in vivo BE data?

A waiver was not requested as bioequivalence of all strengths were assessed, (b) (4)

2.5.3 Has relative bioavailability been established with any other formulation? If yes, are they bioequivalent?

Relative bioavailability has been established for three formulations: two clinical trial tablet formulations oral suspension 50 mg/mL *(Test1)*, tablet strength 200 mg *(Test 2),* and tablet strength 800 mg *(Reference)*. The formulations used were oral suspension 50 mg/mL (formulation C1a), tablet 200 mg (formulation FO), and tablet 800 mg (formulation FC). The FC formulation is also used in the pivotal BE study and has been shown to be bioequivalent to the to-be-marketed formulation, thereby establishing a link between the to-be marketed formulation and the oral suspension. The sponsor is not seeking to market the oral suspension, (b) (4)

The pharmacokinetic parameters of (RS)-licarbazepine for the comparisons and the 90% confidence intervals are given in the Tables below:

Table: Arithmetic Mean (SD) Pharmacokinetic Parameters of (RS)-licarbazepine Following Oral Administration of Three Different Formulations of 800 mg SEP-0002093 (N=18)

	C_{max} (ng/mL)	**t_{max} (h)**	**$AUC_{0-\infty}$ (ng·h/mL)**	**$t_{1/2}$ (h)**
Oral suspension 50 mg/mL (Test 1)	18,048 (4644)	2.2 (1.0-4.0)	325,732 (64,898)	9.69 (1.83)
Tablet 4 X 200 mg (Test 2)	16,007 (4,008)	3.0 (1.5-6.0)	304,219 (66,045)	9.33 (1.79)
Tablet 800 mg (Reference)	17,042 (4,131)	3.1 (1.0-4.0)	301,065 (59,957)	9.40 (1.76)

Table: Geometric Means Ratio (GMR) and 90% Confidence Interval for the Comparison of C_{max} and $AUC_{0-\infty}$ of (RS)-licarbazepine

Pharmacokinetic Parameter	**Point Estimate and CI**	**Test 1 / Reference**	**Test 2 / Reference**
C_{max}	GMR (%) 90% CI	106.7 97.0;115.3	94.1 86.1;102.3
$AUC_{0-\infty}$	GMR (%) 90% CI	109.2 101.2;115.4	99.3 94.2;107.4

Bioequivalence criteria between the formulations in comparison were met because the 90% confidence interval for both parameters under consideration ($AUC_{0-\infty}$ and C_{max}) is contained within the 80 - 125% interval.

A slight (but statistically significant) decrease on t_{max} was observed when *Test 1* was compared with *Test 2* formulations. With *Test 1*, median t_{max} occurred at 2.0 h post-dose, and with *Test 2* and *Reference* formulations it occurred at 3.0 h post-dose. No difference was found between t_{max} when *Test 2* was compared with the *Reference* formulation.

In conclusion, *Test 1* (oral suspension 50 mg/mL) and *Test 2* (tablets 200 mg) formulations of SEP-0002093 showed a similar bioavailability in comparison with the *Reference* formulation (tablet 800 mg) and these formulations can be considered to be bioequivalent.

2.5.4 Has dosage strength equivalence been established between different strengths of the to-be marketed formulation? If yes, are they bioequivalent?

Two Tablets of 400 mg are bioequivalent to one Tablet of 800 mg (to-be-marketed formulation). The pharmacokinetic parameters of (RS)-licarbazepine for the two comparisons and the 90% confidence intervals are given in the Tables below:

Table: Arithmetic Mean (SD) Pharmacokinetic Parameters of (RS)-licarbazepine Following a Single SEP-0002093 800 mg Dose in the Form of 1 x 800 mg Tablet (Reference) and in the Form of 2 x 400 mg Tablets (Test) (N=18)

	C_{max}	**t_{max}**	**$AUC_{0-\tau}$**	**$AUC_{0-\infty}$**	**$t_{1/2}$**
	(ng/mL)	**(h)**	**(ng·h/mL)**	**(ng·h/mL)**	**(h)**
1 tablet 800 mg (Reference)	11,288	3	246,504	248,638	10.2
	(2,628)	(1-6)	(50,381)	(50,464)	(1.36)
2 tablets 400 mg (Test)	11,353	2	246,973	249,429	10.2
	(2,748)	(1-6)	(48,599)	(48,873)	(1.51)

Table: Geometric Means Ratio (GMR) and 90% Confidence Interval for the Comparisons

Pharmacokinetic Parameter	**Point Estimate and CI**	**2 x 400 mg (Test) / 1 x 800 mg (Reference)**
C_{max}	GMR (%) 90% CI	100.78 93.91; 108.16
$AUC_{0-\tau}$	GMR (%) 90% CI	100.37 97.82; 102.99

$AUC_{0-\infty}$	GMR (%) 90% CI	100.48 97.91; 103.13

Bioequivalence criteria between *Test* and *Reference* were met because the 90% confidence interval for all parameters under consideration (AUC0-∞, AUC0-t, and Cmax) is contained within the 80-125% interval.

In conclusion, the bioavailability of (RS)-licarbazepine is similar when an SEP-0002093 800 mg oral dose is administered in the form of one 800 mg tablet or in the form of two 400 mg tablets.

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of eslicarbazepine acetate in relation to meals or meal types?

The effect of food on the pharmacokinetic parameters of (RS)-licarbazepine using achiral assay was investigated on the to-be marketed formulation (highest strength 800mg) as well as a clinical trial formulation (4x200 mg).

Food does not affect the AUC and Cmax of (RS)-licarbazepine. The pharmacokinetic parameters and 90% confidence interval to assess the effect of food on the highest strength (800 mg) of the to-be marketed formulation is shown in the following Tables:

Table: Arithmetic Mean (SD) Pharmacokinetic Parameters of (RS)-licarbazepine Following a Single SEP-0002093 800 mg Dose in Fasting (Reference) and Following a Standard Meal (Test) (N=18)

	C_{max} (ng/mL)	**t_{max} (h)**	**$AUC_{0-\tau}$ (ng·h/mL)**	**$AUC_{0-\infty}$ (ng·h/mL)**	**$t_{1/2}$ (h)**
Reference (fasting)	11,288 (2,628)	3 (1-6)	246,504 (50381)	248,638 (50,464)	10.2 (1.36)
Test (standard meal)	11,299 (2,495)	3 (1-8)	239,066 (50,510)	241,074 (50,764)	10.2 (1.13)

Table: Geometric Means Ratio (GMR) and 90% Confidence Interval for the Comparison

Pharmacokinetic Parameter	**Point Estimate and CI**	**Fed (Test) / Fasting (Reference)**

C_{max}	GMR (%) 90% CI	100.96 94.08; 108.35
$AUC_{0-\tau}$	GMR (%) 90% CI	96.79 94.34; 99.32
$AUC_{0-\infty}$	GMR (%) 90% CI	96.75 94.27; 99.29

In conclusion, the presence of food did not change the pharmacokinetics of (RS)-licarbazepine and Eslicarbazepine acetate can be taken without regard to meals.

2.5.6 How do the pharmacokinetics of Eslicarbazepine acetate compare to the approved product Trileptal® (oxcarbazepine)?

Eslicarbazepine and Trileptal® have the same active moieties and are chemically related. SEP-0002093 is extensively metabolized to eslicarbazepine. (R)-licarbazepine and oxcarbazepine were the minor metabolites. SEP-0002093 is not detectable in plasma. Oral oxcarbazepine (Trileptal®) is also metabolized to 2 major metabolites: eslicarbazepine and (R)-licarbazepine. These metabolites are collectively known as the licarbazepine or 10-monohydroxy metabolites (MHD).

Eslicarbazepine from SEP-0002093 has higher exposure compared to that from Trileptal® both after single and multiple doses, although the sum of eslicarbazepine and (R)-licarbazepine was similar after multiple doses. But on molar bases, SEP-0002093 represented a 15% lower dose than Trileptal®.

Pharmacokinetic comparisons of eslicarbazepine acetate and Trileptal® (oxcarbazepine) were conducted in a crossover study after single doses and multiple doses.

<u>After single Dose:</u>
In the single dose study, the subjects received either 900 mg of SEP-0002093 (3,037 μmol) or 900 mg of oxcarbazepine (3,568 μmol). In molar terms, 900 mg of SEP-0002093 represents a 15% lower dose than 900 mg of oxcarbazepine (the molecular weight of SEP-0002093 is 296 and that of oxcarbazepine is 252).

The main pharmacokinetic parameters of eslicarbazepine, (R)-licarbazepine and oxcarbazepine following a single 900 mg oral dose of SEP-0002093 and oxcarbazepine are presented in the following Table:

Table: Mean (SD) pharmacokinetic parameters of eslicarbazepine and (R)-licarbazepine following a single oral dose of 900 mg of SEP-0002093 or Oxcarbazepine or Trilpetal®

	900 mg SEP-0002093, single-dose, p.o.		900 mg Oxcarbazepine, single-dose, p.o.	
	C_{max} (µg/mL)	**$AUC_{0-\infty}$ (µg·h/mL)**	**C_{max} (µg/mL)**	**$AUC_{0-\infty}$ (µg·h/mL)**
Eslicarbazepine	15.8 (3.8)	301.7 (63.9)	6.0 (1.1)	220.5 (46.1)
(R)-Licarbazepine	0.4 (0.09)	16.8 (3.6)	1.7 (0.8)	52.6 (19.9)
Oxcarbazepine	0.14 (0.03)	3.4 (2.00	1.2 (0.6)	8.9 (4.8)

The percentage of total systemic exposure when given SEP-0002093 or Trileptal® is given in the following Table:

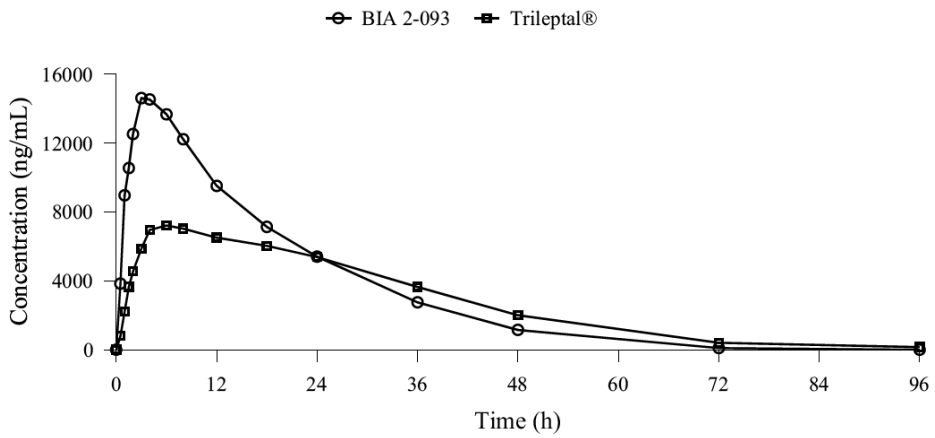
Table. Percentage of total systemic exposure (as assessed by AUC0-t)

	BIA 2-093 (900 mg)	Trileptal (900 mg)
BIA 2-194	95.04%	80.08%
BIA 2-195	4.41%	17.7%
Oxcarbazepine	0.55	2.22%

This table shows that SEP-0002093 has higher systemic exposure to the S-licarbazepine, but less of R-licarbazepine and oxcarbazepine.

Since SEP-0002093 (BIA2-093) is chemically related with Oxcarbazepine and its 10-monohydroxy (MHD, Licarbazepine) metabolite is a mixture of BIA 2-194 (S-Licarbazepine) and BIA 2-195 (R-Licarbazepine), the comparison of their PK profiles of MHD was also conducted.
Mean concentration versus time profiles of [BIA 2-194 plus BIA 2-195] following administration of SEP-0002093 and Trileptal® are illustrated in the following Figure.

Figure. Mean plasma [BIA 2-194 plus BIA 2-195] concentration-time profiles following oral administration of 900 mg of BIA 2-093 or Trileptal®



Ratios between BIA 2-093 metabolites and Trileptal® metabolites after single dose was calculated for Cmax and AUC0-t and summarized in the following Table.

Table . Ratios between Cmax and AUC0-t of [BIA 2-194 plus BIA 2-195] obtained following a single oral dose of 900 mg of BIA 2-093 or Trileptal® (n=12)

	C_{max} [BIA 2-194 + BIA 2-195] (ng/mL)	AUC_{0-t} [total] (ng.h/mL)	AUC_{0-t} [BIA 2-194 + BIA 2-195] (ng.h/mL)
BIA 2-093 (A)	15505	308500	308207
Trileptal® (B)	7471	261970	258493
Ratio A/B	2.08	1.18	1.19

After multiple doses: Ratios between BIA 2-093 metabolites and Trileptal® metabolites after multiple doses for 8 days were calculated for Cmax and AUC0-t and summarized in the following Table.

Ratio between the BIA 2-194, BIA 2-195 and OXC $AUC_{0-\tau}$ (AUC_{0-24h})

	OXC	BIA 2-194	BIA 2-195	Sum
BIA 2-093 900 mg od (A)	3030 ng.h/mL (0.99%)	288280 ng.h/mL (94.64%)	13299 ng.h/mL (4.37%)	304609 ng.h/mL (100%)
Trileptal® 450 mg bid (B)	7694 ng.h/mL (2.57%)	244452 ng.h/mL (81.55%)	47604 ng.h/mL (15.88%)	299750 ng.h/mL (100%)
Ratio A/B	0.39	1.18	0.28	1.02

Although 900 mg of SEP-0002093 represents a 15% lower dose than 900 mg of oxcarbazepine, the extent of systemic exposure expressed as the total AUC of the two active entities (eslicarbazepine and (R)-licarbazepine) was 19% higher following single oral administration of SEP-0002093 (900 mg) than following administration of oxcarbazepine (900 mg) and similar following multiples doses.

Altogether, the results suggest that SEP-0002093 has a higher oral bioavailability of eslicarbazipine than oxcarbazepine.

The recommended dose of Trileptal® for adjunct therapy in partial seizures is also 1200 mg/day. Since the pharmacokinetics of eslicarbazepine is approximately linear, the magnitude of higher systemic exposure with the highest dose of SEP-0002093 (1200 mg/day) will be similar to that observed in these studies.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation for all methods was acceptable.

The following two methods/approaches were used to assess eslicarbazepine acetate or SEP-0002093 or BIA-2-093 and its metabolites:

1. Chiral Method: This distinguishes between eslicarbazepine and its (R)-enantiomer ((R)-licarbazepine).
2. Achiral Method: This does not allow the separation of eslicarbazepine and (R)-licarbazepine, and the enantiomeric mixture has been reported as (RS)-licarbazepine (BIA2-005).

Following administration of SEP-0002093 in humans, exposure to eslicarbazepine is 22 times higher than that of (R)-licarbazepine. Therefore, (RS)-licarbazepine concentrations primarily represent eslicarbazepine, as (R)-licarbazepine is present only in small amounts in the systemic circulation.

The analytical methods used for the assay of SEP-0002093 and its metabolites in plasma and urine consisted of:

1. solid phase extraction followed by high performance liquid chromatography with UV (HPLC-UV) or
2. solid phase extraction followed by liquid chromatography with mass spectrometric detection (LC-MS)
3. solid phase extraction followed by liquid chromatography with mass spectrometric detection (LC-MS/MS) and
4. Liquid-Liquid extraction with mass spectrometric detection (LC-MS/MS)

Matrix	Method	Validation Parameters
Plasma	HPLC-UV- achiral	LLOQ: 20 ng/ml for SEP-0002093 10 ng/ml for (RS)-licarbazepine and Oxcarbazepine Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 20 – 5,000 ≤ 6.8 -5.0 to 1.7 (RS)-Licarbazepine: 10 – 5,000 ≤ 5.7 -1.1 to 2.2 Oxcarbazepine: 10 – 5,000 ≤ 6.2 -2.7 to 5.0
	LC-MS- achiral	LLOQ:10 ng/ml for all moieties Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 10 – 1,000 ≤ 6.6 -8.6 to -5.2 (RS)-Licarbazepine: 10 – 1,000 ≤ 6.5 -1.2 to 3.0 Oxcarbazepine: 10 – 1,000 ≤ 8.4 -5.2 to -1.7 Samples also diluted 20-fold as well Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 10 – 25,000 ≤ 4.5 -3.2 to 3.3 (RS)-Licarbazepine: 10 – 25,000 ≤ 6.1 -3.2 to 3.7
	LC/MS/MS-chiral	LLOQ: 50 ng/ml for SEP-0002093 (S)-licarbazepine, (R)-licarbazepine and oxcarbazepine Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 50 – 1,000 ≤ 3.9 -1.8 to 3.4 Eslicarbazepine: 50 – 25,000 ≤ 8.1 -2.0 to 2.4

		(R)-licarbazepine: 50 – 25,000 ≤ 5.9 -2.3 to 3.1 Oxcarbazepine: 50 – 1,000 ≤ 14.3 -0.7 to 12.9
Urine	LC-MS- achiral	LLOQ:10 ng/ml for all moieties Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 10 – 1,000 ≤ 8.8 -1.4 to 2.7 (RS)-Licarbazepine: 10 – 1,000 ≤ 9.2 0.5 to 4.7 Oxcarbazepine: 10 – 1,000 ≤ 9.2 -8.8 to -3.3 Samples also diluted 10-fold
	LC/MS/MS-chiral	LLOQ: 50 ng/ml for SEP-0002093 (S)-licarbazepine, (R)-licarbazepine and oxcarbazepine Analyte Curve range (ng/mL) CV% RE% SEP-0002093: 50 – 1,000 ≤ 5.9 3.4 to 8.9 Eslicarbazepine: 50 – 25,000 ≤ 7.3 6.0 to 13.2 (R)-licarbazepine: 50 – 25,000 ≤ 7.1 4.9 to 8.9 Oxcarbazepine: 50 – 1,000 ≤ 7.7 5.9 to 9.2

Stability: Short Term

Type of Stability	Matrix	Storage Condition	Analyte	Established Stability
Freeze-Thaw	Plasma	-20 °C	SEP-0002093	3 cycles
			Eslicarbazepine	3 cycles
			(R)-licarbazepine	3 cycles
			(RS)-Licarbazepine	3 cycles
			Oxcarbazepine	3 cycles
	Urine	-20 °C	SEP-0002093	3 cycles
			Eslicarbazepine	3 cycles
			(R)-licarbazepine	3 cycles
			(RS)-Licarbazepine	3 cycles
			Oxcarbazepine	3 cycles

Type of Stability	Matrix	Storage Condition	Analyte	Established Stability
Bench-Top	Plasma	Room Temperature	SEP-0002093	Up to 24 h
			Eslicarbazepine	Up to 24 h
			(R)-licarbazepine	Up to 24 h
			(RS)-Licarbazepine	Up to 24 h
			Oxcarbazepine	Up to 24 h
	Urine	Room Temperature	SEP-0002093	Up to 24 h
			Eslicarbazepine	Up to 24 h

			(R)-licarbazepine	Up to 24 h
			(RS)-Licarbazepine	Up to 24 h
			Oxcarbazepine	Up to 24 h

Extracted Sample	Plasma Extracts	4°C / RT	SEP-0002093	Up to 96 h
			Eslicarbazepine	Up to 48 h
			(R)-licarbazepine	Up to 48 h
			(RS)-Licarbazepine	Up to 96 h
			Oxcarbazepine	Up to 48 h
	Urine Extracts	4°C and RT	SEP-0002093	Up to 24 h
			(RS)-Licarbazepine	Up to 24 h
			Oxcarbazepine	Up to 24 h
Re-injection Reproducibility	Plasma Extracts	10°C	SEP-0002093	Up to 41 h
			Eslicarbazepine	Up to 41 h
			(R)-licarbazepine	Up to 41 h
			Oxcarbazepine	Up to 41 h
	Urine Extracts	10°C	SEP-0002093	Up to 45 h
			Eslicarbazepine	Up to 45 h
			(R)-licarbazepine	Up to 45 h
			Oxcarbazepine	Up to 45 h

Stability: Long Term

Type of Stability	Matrix	Storage Condition	Analyte	Established Stability
Long-term	Plasma	-20°C	SEP-0002093	Up to 31 months
			Eslicarbazepine	Up to 31 months
			(R)-licarbazepine	Up to 31 months
			(RS)-Licarbazepin	75 days
			Oxcarbazepine	Up to 8 days
	Urine	-20°C	SEP-0002093	Up to 28 months
			Eslicarbazepine	Up to 28 months

			(R)-licarbazepine	Up to 28 months
			Oxcarbazepine [b]	Up to 35 days

All plasma and urine samples were analyzed within these time frames.

3.0 DETAILED LABELING RECOMMENDATION

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.1 APPENDIX I

4.1.1 INDIVIDUAL STUDY REVIEW

PK IN HEALTHY SUBJECTS:

Study 101: A single centre, Phase I, double-blind, randomized, placebo-controlled study to investigate the safety, tolerability, pharmacokinetic profile and effects on EEG of single rising oral doses of BIA 2-093 when given to healthy male adult volunteer

Objectives:

- To investigate the safety and tolerability of single rising oral doses of BIA 2-093 ([redacted] (b) (4) 20mg, 50mg, 100mg, 200mg, 400mg, 600mg, 900mg and 1200 mg) in groups of 8 healthy male adult volunteers.
- To characterize the preliminary pharmacokinetics of single rising oral doses of BIA 2-093 in healthy male adult volunteers.

The study design is as follows:

Study Design	Single centre, Phase I, double-blind, randomized, placebo-controlled study
Study Population	N=64 Healthy subjects Age: 18-35 years Gender: All males Weight: 61-72 kg Race: All Caucasians
Treatment Group	Sequential Groups BIA 2-093 at dose levels of 20mg, 50mg, 100mg, 200mg, 400mg, 600mg, 900mg and 1200mg, administered as oral tablets: 10mg (Batch 00334), 50mg (Batch 00335), 100 mg (Batch 00336) or 200 mg (Batch 00384) with 200 ml potable water.
Dosage and Administration	Within each group of eight subjects two subjects were randomized to receive placebo and the remaining six subjects were randomized to receive BIA 2-093. No subject was a member of more than one treatment group. Doses of 20mg, 50mg, 100mg, 200mg, 400mg, 600mg, 900mg and 1200mg were investigated in ascending order. Progression to each dose occurred only after the previous dose level was deemed to be safe and well tolerated by the investigator and the sponsor. Diet: Overnight fast Washout: 5 days between two treatments
Sampling: Blood	For plasma BIA 2-093 and metabolites: At Pre dose, 15, 30, 45, 60, 90, 120, 150, 180 minutes, 4, 5, 6, 7, 8, 10, 12, 16, 24, 30, 36 and 48 hours post dose.

Urine	For plasma BIA 2-093 and metabolites: Pre dose, 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hours post dose.
Feces	none
Analysis	Lower Limits of Quantitation Plasma / Urine BIA 2-093: 20 ng/ml / 20 ng/ml BIA 2-005: 10 ng/ml / 10 ng/ml Oxcarbazepine: 10 ng/ml / 10 ng/ml Plasma: Method: HPLC/ UV method Linear Range: 20-5000 ng/ml in plasma for BIA 2-093 10 - 5000 ng/ml for BIA 2-005 and oxcarbazepine Quality control concentrations: 50, 500, 4000 ng/ml for BIA 2-093 25, 500, 4000 ng/ml for BIA 2-005 and oxcarbazepine Inter-day precision: % CV: 2 % to 10 % for BIA 2-093, from 6.2 % to 8.3 % for BIA 2-005 and from 4.2 % to 8.1 % for oxcarbazepine Inter-day accuracy: –7.1 % to –3.3 % for BIA 2-093, from –4.2 % to 3.4 % for BIA 2-005 and from –9.2 % to –2.8 % for oxcarbazepine. Urine: Method: LC/MS/MS method Linear Range: 20-1000 ng/ml in urine for BIA 2-093 10 - 1000 ng/ml for BIA 2-005 and oxcarbazepine Quality control concentrations: 25, 100 and 800 ng/ml for all Inter-day precision: % CV: 4.6% to 8.8% for BIA 2-093, from 5.2% to 9.8% for BIA 2-005 and from 5.2% to 5.6% for oxcarbazepine Inter-day accuracy: 0% to 2.9% for BIA 2-093, from 5.1% to 14.1% for BIA 2-005 and from 6.2% to 11.2% for oxcarbazepine
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, Clr, Ae
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	Pharmaco EEG recordings: At pre dose, 2.5 and 6.5 hours post dose

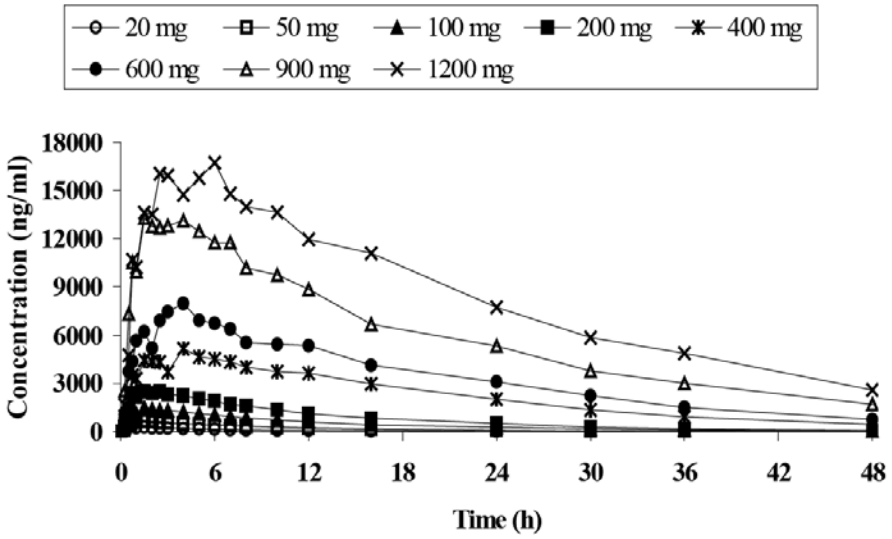
Pharmacokinetic Results:

In Plasma:

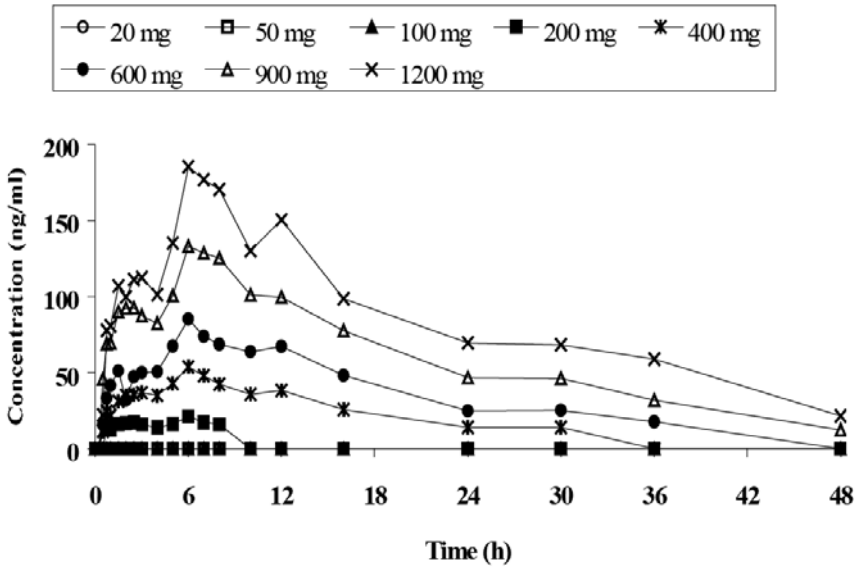
Pharmacokinetic parameters were not determined for BIA 2-093 as concentrations were below the limit of quantification of the assay.

The mean plasma concentration profiles for BIA 2-05 and oxycarbazepine are shown in the following Figures:

Mean Plasma BIA 2-005 Concentration-Time Profiles Following Oral Administration of 20, 50, 100, 200, 400, 600, 900 and 1200 mg BIA 2-093



Mean Plasma Oxcarbazepine Concentration-Time Profiles Following Oral Administration of 20, 50, 100, 200, 400, 600, 900 and 1200 mg BIA 2-093



The mean pharmacokinetic parameters are shown in the following Tables:

Mean (COV) Pharmacokinetic Parameters of BIA 2-005 Following Oral Administration of 20, 50, 100, 200, 400, 600, 900 and 1200 mg BIA 2-093

			BIA 2-005		
Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	$t_{1/2}$ (h)	CL_r (ml/min)
20	349	0.75	2421	9.07	19.2
	(18.7)	(0.5-0.75)	(16.2)	(15.9)	(21.4)
50	948	0.75	6664	8.08	19.5
	(24.7)	(0.5-2)	(12.7)	(9.07)	(21.4)
100	1536	1.5	16355	9.28	17.4
	(13.8)	(0.5-2)	(11.7)	(8.71)	(22.9)
200	2884	1.5	30503	8.37	22.9
	(16.2)	(0.75-2.5)	(23.7)	(18.8)	(19.8)
400	5193	4	81536	11.7	16.2*
	(11.6)	(4-5)	(10.8)	(18.6)	(17.5)
600	8489	4	119717	12.3	18.4*
	(20.0)	(0.5-5)	(17.4)	(14.8)	(18.8)
900	14595	2.25	210281	16.3	18.9
	(18.2)	(0.75-4)	(10.6)	(31.9)	(14.3)
1200	18579	4	285626	16.5	15.9
	(16.3)	(2-6)	(16.7)	(6.83)	(21.1)

t_{max} values are median with range of values in parentheses
n=6 per dose group; * n=5

Mean (COV) Pharmacokinetic Parameters of Oxcarbazepine Following Oral Administration of 20, 50, 100, 200, 400, 600, 900 and 1200 mg BIA 2-093

		Oxcarbazepine		
Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	$t_{1/2}$ (h)
20	NC#	NC#	NC#	NC#
50	NC#	NC#	NC#	NC#
100	13.6*	6*	83.9**	NC
	(17.0)	(0.75-7)	(40.4)	
200	23.2	6	198	6.84
	(15.3)	(0.75-7)	(45.1)	(42.4)
400	54.7	6	736	12.6
	(17.2)	(6-7)	(9.32)	(21.8)
600	85.9	6	1228	13.6*
	(31.4)	(6-8)	(23.1)	(16.5)
900	136	6	2053	14.3
	(17.6)	(6-8)	(15.8)	(16.3)
1200	189	6	2736	14.2*
	(12.8)	(6-8)	(10.4)	(13.4)

t_{max} values are median with range of values in parentheses
NC# = Not calculated; insufficient measurable concentrations,

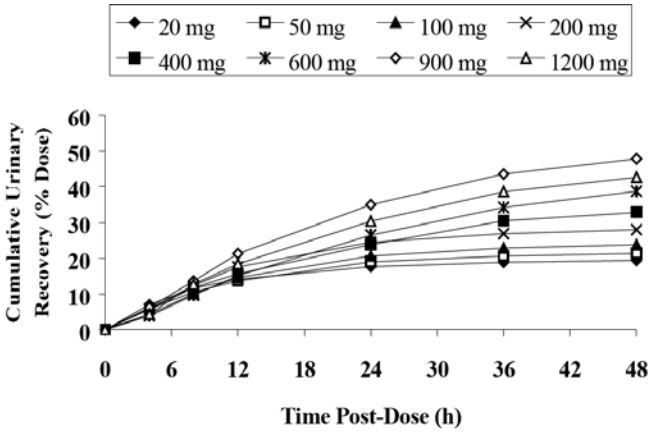
- AUC0-∞ was not used to assess dose-proportionality because these estimates were considered to be less reliable than AUC0-τ (extrapolated area was generally greater than 20% of the total AUC for oxcarbazepine).
- The kinetics of the metabolites BIA 2-005 and oxcarbazepine appeared to be nonlinear with respect to dose over the dose range 100 to 1200 mg BIA 2-093, i.e., dose dependent.

- For the metabolite BIA 2-005, over the dose range of 20 to 1200 mg, there was a statistically significant greater than dose-proportional increase in AUC0-τ values. The value of the exponent (95% CI) for AUC0-τ was 1.17 (1.14, 1.20). By contrast, Cmax increased in slightly less than dose proportional manner over the dose range studied. The value of the exponent of the power function (95% CI) for Cmax was 0.95 (0.91, 0.99).
- Maximum plasma concentrations of a metabolite, BIA 2-005 were on average attained at 0.75 to 4 h post-dose. Thereafter, plasma BIA 2-005 concentrations declined with a mean apparent terminal half-life of approximately 8 to 17 h.
- For the metabolite oxcarbazepine, over the dose range of 100 to 1200 mg, the increase in AUC0-τ and Cmax values was statistically significantly greater than dose proportional. The value of the exponent of the power function (95% CI) for AUC0- τ was 1.49 (1.35, 1.62). The value of the exponent of the power function (95% CI) for Cmax was 1.09 (1.01, 1.17).

In Urine:

- Urinary recovery of BIA 2-093 and oxcarbazepine was low (less than 1 % of the administered dose). Recovery of BIA 2-005 in urine was approximately 19% of the administered dose following 20 mg BIA 2-093 and increased with increasing dose to approximately 40 to 50% of the administered dose following 900 and 1200 mg BIA 2- 093. This apparent dose-dependent increase in urinary recovery was also evident for the metabolite oxcarbazepine. The cumulative urinary excretion of BIA 2-005 is shown in the following Figure:

Mean Cumulative Urinary Excretion of BIA 2-005 Following Oral Administration of 20, 50, 100, 200, 400, 600, 900 and 1200 mg BIA 2-093



- Renal clearance of BIA 2-005 following a single oral dose of 20 to 1200 mg BIA 2-093 was approximately 20 ml/min irrespective of the dose given, which is low compared with glomerular filtration rate (127 ml/min). Reliable estimates of renal

clearance of BIA 2-093 and oxcarbazepine could not be determined due to minimal recovery of these analytes in urine.

Safety:

The incidence of adverse events was similar between all treatment groups. Reported treatment-emergent adverse events which were considered to be possibly related to treatment were: headache, somnolence, dizziness, abdominal pain; and the following occurred once each in subjects receiving BIA 2-093: dry mouth, nausea, agitation, eye strain, and sore throat.

Overall Conclusions:

Parent: Following single oral doses of BIA 2-093 at 20, 50, 100, 200, 400, 600, 900 and 1200 mg to healthy male subjects, BIA 2-093 appeared to be metabolized to BIA 2-005 and oxcarbazepine with, in general, no measurable concentrations of BIA 2-093 observed at the dose levels studied.

Metabolite BIA 2-005: The increase in systemic exposure of BIA 2-005 with the increase in dose was significantly less than proportional to the administered dose for Cmax and was greater than dose proportional for AUC0-τ. The tmax was attained at 0.75 to 4 h post-dose and had a half-life of approximately 8 to 17 h. There was a dose-dependent increase in urinary recovery that is consistent with the greater than dose-proportional increase in systemic exposure to BIA 2-005 in plasma.

Metabolite oxacrbazepine: The increase in systemic exposure was significantly greater than proportional to the administered dose for Cmax and AUC0-τ. The tmax was attained at 6 h post-dose and had a half-life of approximately 7 to 14 h. Less than 1% of the administered dose was recovered in the urine.

Study 102: A double-blind, randomized, placebo-controlled, rising multiple dose study to investigate the safety, tolerability, steady state pharmacokinetic profile and CNS effects of BIA 2-093, in young healthy male volunteers.

Objectives:

To investigate the safety and tolerability of multiple dose regimens of BIA 2-093 in healthy young male volunteers. And to characterize the steady state pharmacokinetic profile of BIA 2-093 in healthy young male volunteers.

The study design is as follows:

Study Design	Single centre, Phase I, double-blind, randomized, placebo-controlled study
Study Population	N=32 Healthy subjects Age: 18-45 years Gender: All males Weight: 58.5- 100.9 kg (mean 74 kg) Race: All Caucasian
Treatment Group	Group 1: 200 mg b.i.d. (doses were given on days 1-7, with single dose of Day 8) Group 2: 400mg qd qd for 8 days Group 3: 800 mg qd for 8 days Group 4: 1200 mg qd for 8 days 200 mg (Batch 00383) with 200 ml potable water.
Dosage and Administration	Within each group of eight subjects two subjects were randomized to receive placebo and the remaining six subjects were randomized to receive BIA 2-093. No subject was a member of more than one treatment group. Diet: Meals were served as follows: Days 1 and 8 – no breakfast, lunch 4 hours post dose and dinner 10 hours post dose. Days 2-7 - breakfast 1 hour post dose, lunch 4 hours post dose and dinner 10 hours post dose.
Sampling: Blood	For plasma BIA 2-093 and metabolites: BIA 2-005 and oxcarbazepine: Pre-a.m. dose, 30, 60, 90, 120, 180 minutes, 4, 6, 7, 8, 12 hours post-a.m. dose on day 1; Pre-a.m. dose on days 2-7 inclusively; Pre-dose, 30, 60, 90, 120, 180 minutes, 4, 6, 7, 8, 12, 24, 36, 48 and 72 hours post final dose on day 8.
Urine	For urine BIA 2-093 and metabolites: Pre-a.m. dose, 0-4, 4-8, 8-12, 12-24 hours post-a.m. dose on day 1; Pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours post final dose on day 8.
Feces	none
Analysis	

	Lower Limits of Quantitation Plasma Urine BIA 2-093 10 ng/ml 10 ng/ml BIA 2-005 10 ng/ml 10 ng/ml Oxcarbazepine 10 ng/ml 10 ng/ml Plasma: Method: HPLC/ UV method Linear Range: 10-1000 ng/ml in plasma for BIA 2-093, BIA 2-005 and oxcarbazepine Quality control concentrations: 50, 100, 600 ng/ml for BIA 2-093 BIA 2-005 and oxcarbazepine Inter-day precision: % CV: 4.46 % to 6.55 % for BIA 2-093, from 5.11 % to 6.64 % for BIA 2-005 and from 6.05 % to 7.03 % for oxcarbazepine. Inter-day accuracy: –1.58 % to 0.896 % for BIA 2-093, from 4.94 % to 6.90 % for BIA 2-005 and from –0.341 % to 0.722 % for oxcarbazepine. Urine: Method: LC/MS/MS method Linear Range: 10-1000 ng/ml in urine for BIA 2-093; BIA 2-005 and oxcarbazepine Quality control concentrations: 25, 100, 800 ng/ml Inter-day precision: % CV: 4.15 % to 9.55 % for BIA 2-093, from 7.92 % to 12.3 % for BIA 2-005 and from 2.67 % to 7.72 % for oxcarbazepine Inter-day accuracy: 1.80 % to 5.43 % for BIA 2-093, from 0.746 % to 4.16 % for BIA 2-005 and from –1.76 % to 1.35 % for oxcarbazepine
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, R0, Rt, Clr, Ae
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	Pharmaco EEG recordings: At pre dose, 2.5 and 6.5 hours post dose

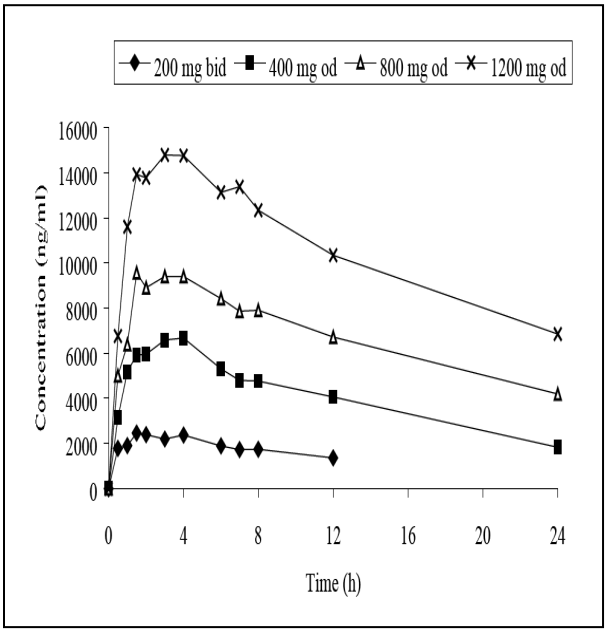
Pharmacokinetic Results:

In Plasma:

Pharmacokinetic parameters were not determined for BIA 2-093 since, in general concentrations were below the limit of quantification of the assay.

The mean plasma concentration profiles for BIA 2-05 and oxycarbazepine for Days 1 and 8 are shown in the following Figures:

Figure. Mean Plasma BIA 2-005 Concentration-Time Profiles Following Oral Administration of 200 mg b.i.d., 400 mg o.d., 800 mg o.d. and1200 mg o.d. BIA 2-093 – Day 1 and Day 8



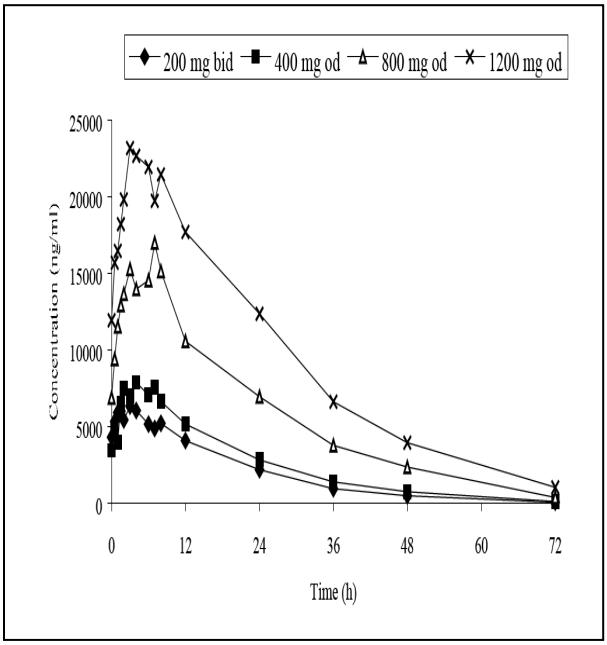
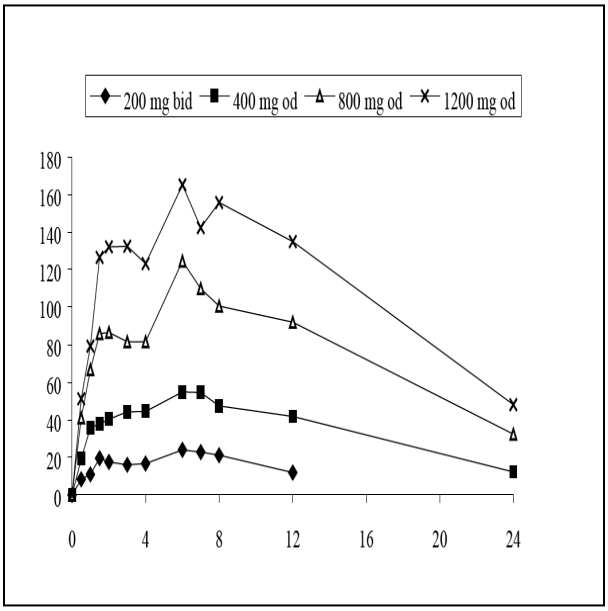
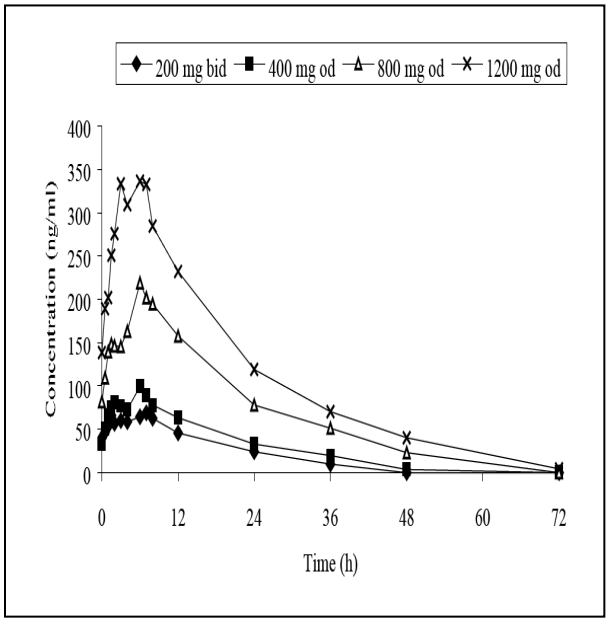


Figure D. Mean Plasma Oxcarbazepine Concentration-Time Profiles Following Oral Administration of 200 mg b.i.d., 400 mg o.d., 800 mg o.d. and 1200 mg o.d. BIA 2-093 – Day 1 and Day 8





The pharmacokinetic parameters are shown in the following Table:

Table. Mean (COV) Pharmacokinetic Parameters of BIA 2-005

Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	$t_{1/2}$ (h)	R_0 (ratio)	CL_R (ml/min)
			Day 1			
200 b.i.d.	3086	2	22163	8.42#	-	26.2
	(43.5)	(0.5-4)	(28.0)	(26.8)	-	(20.6)
400 o.d.	7827	1.75	96262	12.7*	-	21.7
	(16.8)	(1-4)	(17.7)	(32.5)	-	(34.4)
800 o.d.	11074	3	159492	21.4*	-	27.8
	(17.3)	(1.5-7)	(13.6)	(60.4)	-	(27.9)
1200 o.d.	16071	1.75	250426	15.8*	-	28.9
	(13.9)	(1-7)	(10.9)	(15.1)	-	(23.0)
			Day 8			
200 b.i.d.	6683	2.75	63140	9.40	2.95	23.2
	(23.6)	(1-4)	(12.7)	(16.7)	(16.9)	(14.9)
400 o.d.	8824	3	126308	9.50	1.36	26.2
	(16.0)	(0.5-7)	(11.7)	(18.8)	(28.3)	(32.1)
800 o.d.	18675	2.5	268384	12.3	1.70	20.9
	(14.0)	(1-7)	(10.3)	(22.9)	(11.4)	(24.0)
1200 o.d.	25457	3	423003	13.1	1.70	27.0*
	(10.8)	(0.5-6)	(10.9)	(20.1)	(10.8)	(18.8)*

t_{max} values are median with range of values in parentheses
n=6 per dose group unless otherwise noted: * n=5, # n=3

Table. Mean (COV) Pharmacokinetic Parameters of Oxcarbazepine

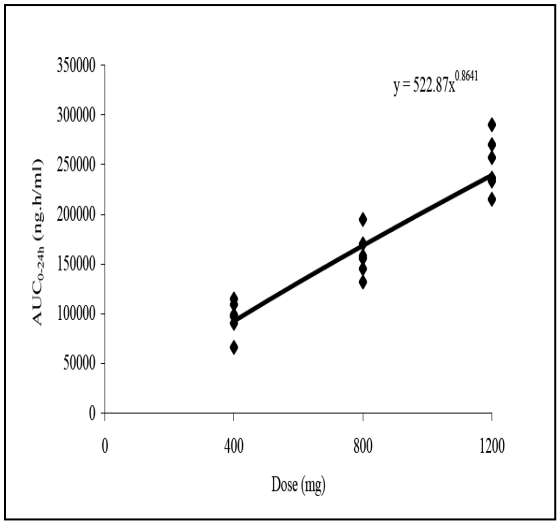
Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/ml)	$t_{1/2}$ (h)	R_0 (ratio)
			Day 1		
200 b.i.d.	26.7	7	208	5.51*	-
	(30.0)	(1.5-8)	(30.8)	(32.2)	-
400 o.d.	59.2	6.5	849	8.04**	-
	(10.7)	(1-8)	(11.8)	(15.4)	-
800 o.d.	126	6	1840	9.24*	-
	(15.3)	(6-7)	(13.1)	(10.7)	-
1200 o.d.	197	6	2685	8.10#	-
	(43.6)	(1.5-8)	(15.6)	(22.1)	-
			Day 8		
200 b.i.d.	78.2	7	698	12.7	3.38
	(43.2)	(1.5-7)	(35.7)	(18.6)	(14.1)
400 o.d.	102	3	1488	14.2	1.79
	(15.2)	(1-6)	(27.2)	(17.5)	(33.5)
800 o.d.	227	6	3464	13.3	1.85
	(28.6)	(1.5-6)	(33.5)	(13.1)	(21.7)
1200 o.d.	376	5	5480	14.1	2.05
	(19.6)	(1-8)	(19.1)	(10.6)	(16.5)

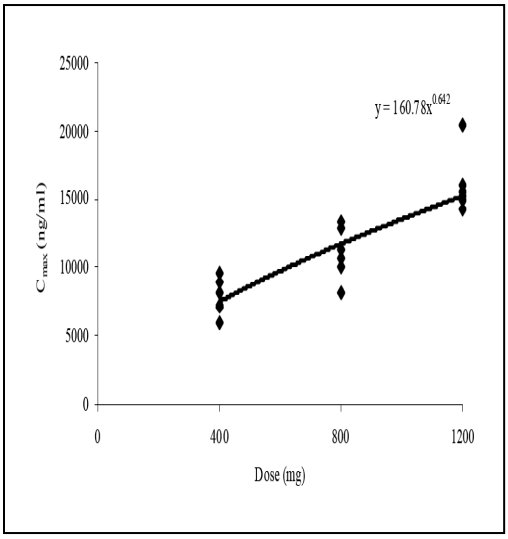
t_{max} values are median with range of values in parentheses
n=6 per dose group unless otherwise noted: * n=5, ** n=4, # n=2

BIA 2-005

- Tmax of BIA 2-005 was reached on average at 2 to 3 h post-dose. Plasma concentrations of BIA 2-005 declined with an approximate mean apparent terminal half-life of 8 to 21 h following a single dose and 9 to 13 h following repeated administration.
- Following single and repeated oral administration of BIA 2-093, for the metabolite BIA 2-005, the exponent values for AUC0-24h and Cmax were 0.9 (CI 0.70, 1.03) to 1.1 (CI 0.98, 1.22) and 0.6 (CI 0.46, 0.82) to 1.0 (CI 0.83, 1.30), respectively. Overall, the extent of systemic exposure to BIA 2-005 tended to increase in an approximately dose proportional manner over the dose range of 400 to 1200 mg BIA 2-093 (See figures below that shows dose proportionality on Day 1)

Relationship between AUC0-24h and Cmax Values of BIA 2-005 and Dose (day 1)





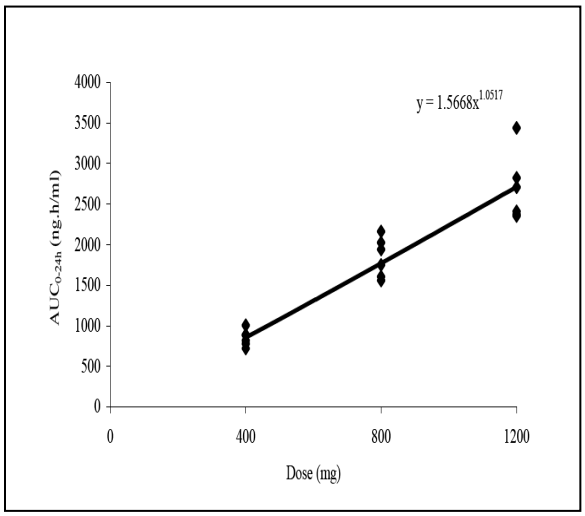
- The mean observed accumulation ratio (Ro) for BIA 2-005 was 3.0, consistent with the t1/2.
- It attained steady-state levels after approximately 4 to 5 days of repeated once- or twice daily dosing.
- Between-subject (inter individual) variability in the extent of systemic exposure (AUC) to BIA 2-005 was relatively low, with coefficients of variation ranging from 10 to 30 %

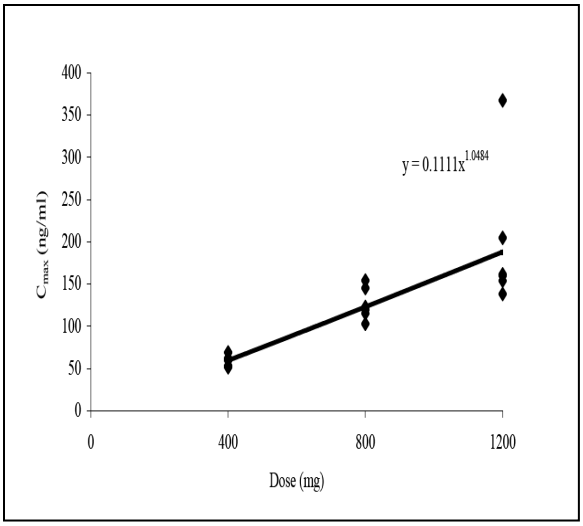
Oxcarbazepine

- Maximum plasma concentrations of oxcarbazepine were reached on average 3 to 7 h post-dose. Plasma concentrations of oxcarbazepine declined with an approximate mean apparent terminal half-life of 6 to 9 h following a single dose and 13 to 14 h following repeated administration.
- The values of the exponent of the power function for AUC0-24h and Cmax ranged from 1.1 to 1.2, indicating that the extent of systemic exposure tended to

increase in an approximately dose proportional manner over the dose range of 400 to 1200 mg (See Figure below)

Relationship between AUC0-24h and Cmax Values of Oxcarbazepine and Dose (day 1)





- The mean observed accumulation ratio (RO) for oxcarbazepine was 3.0, consistent with the t1/2.
- It attained steady-state levels after approximately 5 days of repeated once- or twice daily dosing of BIA 2-093.
- Between-subject (inter individual) variability in the extent of systemic exposure (AUC) to oxcarbazepine had coefficients of variation ranging from 12 to 38 %.

In Urine:

- Urinary recovery of BIA 2-093 and oxcarbazepine were minimal (less than 1 % of the administered dose).
- Recovery of BIA 2-005 in urine was approximately 20 % of the administered dose up to 12 hours post-dose and 40 % of the administered dose up to 24 hours post-dose.
- Renal clearance of BIA 2-005 from plasma following single and repeated oral administration of BIA 2-093 at all dose levels was approximately 20 to 30 ml/min

Safety:

Most common event were: dizziness, headache, somnolence, gingival bleeding, dyspepsia, dry mouth, nausea, pharyngitis, flushing, muscle contractions involuntary (fasciculation in the thumb), mucositis (catarrh), hepatic enzymes increased (in the 1200 mg group and had the highest plasma exposure: (Cmax and AUC0-τ of 20468 ng/ml and 290208 ng.h/ml), back pain, hallucination (hypnagogic), upper respiratory tract infection, rash, skin dry, and conjunctivitis. Some of the adverse events appeared to be dose related.

Conclusions:

- The extent of systemic exposure to BIA 2-005 increased in an approximately dose-proportional manner following single and repeated administration.

Reviewer's Comment:

The standard curve range was from 10-1000 ng/ml. But plasma concentrations were between 5000-7000 ng/ml. No information is given regarding dilution in the bioanalytical assay.

Study 113: A double-blind, randomized, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetic profile of two single and multiple high dose regimens of BIA 2-093, in healthy volunteers.

Objectives:

- To characterize the single-dose and steady-state pharmacokinetic profile and investigate the tolerability of 1800 mg and 2400 mg of BIA 2-093.

The study design is as follows:

Study Design	Single centre, Phase I, double-blind, randomized, placebo-controlled study
Study Population	N=18 Healthy subjects (9 per group) Age: 20-43 years (mean 25 years) Gender: All males Weight: 57-91 kg (mean 75 kg) Race: All Caucasian
Treatment Group	Group 1: 1800 mg SD and MD for 7 days Group 2: 2400 mg SD and MD for 7 days 600 mg (Batch 040121-L.) with 200 ml potable water.
Dosage and Administration	Within each group of 3 subjects two subjects were randomized to receive placebo and the remaining six subjects were randomized to receive BIA 2-093. No subject was a member of more than one treatment group. Diet: On Day 1 and Day 11, subjects were requested to fast overnight for at least 8 hours before dosing and to remain fasted until 1 hour post-dose; then, a standard breakfast was served. A standard lunch was served about 4 hours after product administration. Wash out: 96 hours between single dose and multiple dose phase
Sampling: Blood	For plasma BIA 2-093 and metabolites: BIA 2-005 and oxcarbazepine: Phase A: pre-dose (Day 1); and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose. Phase B: Days 6 to 10 inclusively: pre-dose. Day 11 (last dose): pre-dose; and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.
Urine	For urine BIA 2-093 and metabolites: *Phase A*, Day 1: pre-dose; and 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84 and 84-96 hours post-dose. *Phase B*, Day 11: pre-dose; and 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84 and 84-96 hours post-dose.
Feces	none
Analysis	Lower Limits of Quantitation

	Plasma Urine BIA 2-093 10 ng/ml 10 ng/ml BIA 2-005 10 ng/ml 10 ng/ml Oxcarbazepine 10 ng/ml 10 ng/ml Plasma: Method: HPLC/ UV method Linear Range: 10-1000 ng/ml in plasma for BIA 2-093, BIA 2-005 and oxcarbazepine Quality control concentrations: 25, 400 and 600 ng/ml for BIA 2-093, 25, 400, 700 and 1000 (diluted various folds) BIA 2-005 and 25, 400, 700 for oxcarbazepine Inter-day precision: % CV: 5.40 % to 7.59 % for BIA 2-093, from 7.25% to 9.96% for BIA 2-005 and from 6.63 % to 7.75 % for oxcarbazepine. Inter-day accuracy: –4.6 % to 0.958 % for BIA 2-093, from -4.53 % to 0.282 % for BIA 2-005 and from –0.983 % to -1.99 % for oxcarbazepine. Urine: Method: LC/MS/MS method Linear Range: 10-1000 ng/ml in urine for BIA 2-093; BIA 2-005 and oxcarbazepine Quality control concentrations: 25, 400, 600 ng/ml for BIA 2-093, 25, 400, 700 and 1000 (diluted various folds) BIA 2-005 and 25, 400, 700 oxcarbazepine Inter-day precision: % CV: 7.39 % to 11.3 % for BIA 2-093, from 2.95 % to 10.5 % for BIA 2-005 and from 7.98% to 8.33 % for oxcarbazepine Inter-day accuracy: 201% to 5.27 % for BIA 2-093, from -2.62 % to 11.4 % for BIA 2-005 and from –2.17 % to 3.82 % for oxcarbazepine
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, R0, Rt, Clr,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

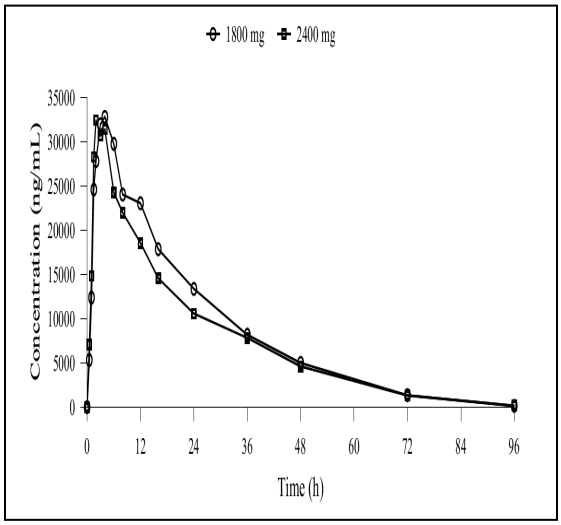
Pharmacokinetic Results:

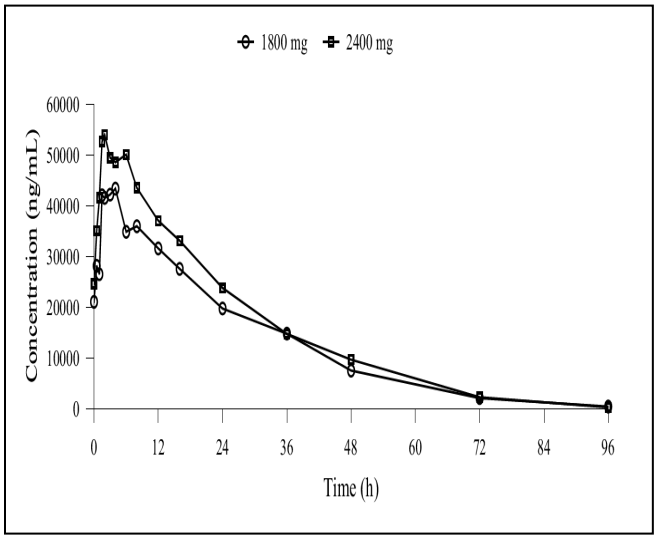
In plasma:

Plasma levels of BIA 2-093 were below the limit of quantification (10 ng/mL) at almost all sampling times.

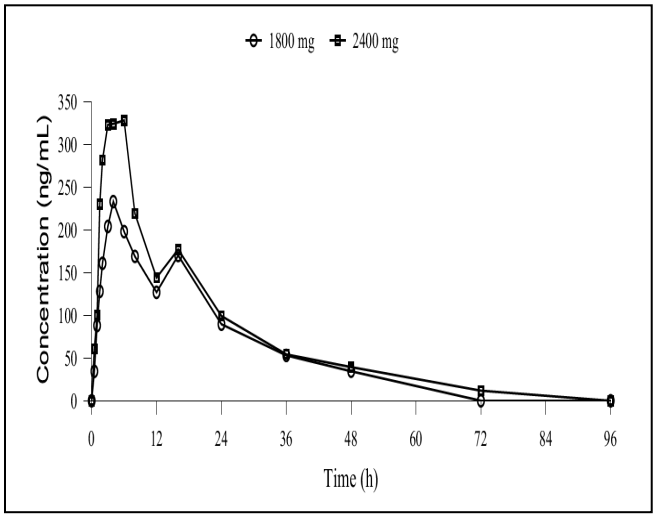
Mean Plasma concentration for BIA 2-005 and oxcarbazepine after SD and on Day 7 of the MD phase are shown in the following figures:

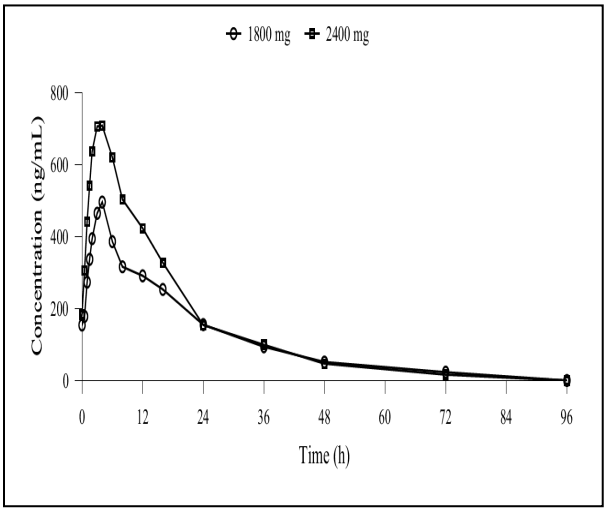
Mean plasma BIA 2-005 concentration-time profiles: SD and Day 7 of MD Phase





Mean plasma oxcarbazepine concentration-time profiles: SD and Day 7 of MD Phase





The pharmacokinetic parameters of BIA 2-005 following single-dose (Day 1) and last dose (Day 11) of a 7-day once-daily regimen of BIA 2-093 1800 mg and 2400 mg are summarized as follows:

Table. BIA 2-005 pharmacokinetic parameters

Dosing regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)	R_0 (ratio)	CL_r (mL/min)
			Day 1			
1800 mg single-dose	34569 (5623)	3.5 (3.0-6.0)	507563 (86363)	11.8 (1.96)	-	20.0 (7.32)
2400 mg single-dose	35926 (15301)	3.0 (1.5-6.0)	445596 (116306)	11.1 (2.35)	-	39.4 (15.3)
			Day 11			
1800 mg once-daily	47665 (11108)	1.8 (0.5-4.0)	740299 (144882)	11.3 (3.26)	1.47 (0.20)	23.8 (10.9)
2400 mg once-daily	56506 (11277)	2.0 (1.5-8.0)	905860 (115783)	10.4 (2.49)	2.13 (0.50)	28.3 (4.88)

Results expressed as arithmetic means with the corresponding standard deviations (sd) in parentheses.
t_{max} values are median with range values in parentheses.

- Following a single dose of BIA 2-093 1800 mg and 2400 mg, no dose-proportional increase in systemic exposure to BIA 2-005 was apparent.
- Following multiple dose of BIA 2-093 1800 mg and 2400 mg, a dose proportional increase in systemic exposure to BIA 2-005 was apparent.
- Mean pre-dose concentrations of BIA 2-005 appeared to attain steady-state levels after approximately 4 to 5 days of repeated daily dosing, which is consistent with an effective half-life in the order of 20-24 hours.

Table. Oxcarbazepine pharmacokinetic parameters

Dosing regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)	R_0 (ratio)	CL_r (mL/min)
			Day 1			
1800 mg single-dose	241 (57)	4.67 (4.0-6.0)	3589 (847)	16.1 (3.78)	-	-
2400 mg single-dose	361 (106)	4.0 (3-6.0)	4547 (1512)	16.8 (2.68)	-	-
			Day 11			
1800 mg once-daily	508 (177)	3.83 (3.0-6.0)	6958 (1824)	14.8 (2.59)	1.94 (0.23)	-
2400 mg once-daily	734 (186)	3.67 (3.0-4.0)	9956 (2329)	12.5 (2.49)	2.36 (0.75)	-

- The observed accumulation is consistent with an effective elimination half-life of approximately 19 to 23 hours.
- Additionally, mean pre-dose concentrations of oxcarbazepine appeared to attain steady-state levels after approximately 5 days of repeated daily dosing, which is consistent with an effective half-life in the order of 24 hours.

In Urine:

- The mean urinary recovery of BIA 2-093 and oxcarbazepine was minimal (less than 1% of the administered dose).
- Recovery of BIA 2-005 in urine up to 24 hours post-dose was approximately 38% following a 1800 mg single-dose and 48% following a 2400 mg single-dose.
- Renal clearance of BIA 2-005 from plasma following single and repeated oral administration of 1800 mg and 2400 mg BIA 2-093 was approximately 20 to 40 mL/min.
- Reliable estimates of renal clearance of BIA 2-093 and oxcarbazepine could not be determined due to minimal recovery of these analytes in urine.

Overall Conclusions:

- Following single oral doses of BIA 2-093 at 1800 mg and 2400 mg, concentrations of BIA 2-093 in plasma and urine were not measurable.
- A dose-proportional increase in systemic exposure to BIA 2-005 was apparent following multiple dose of BIA 2-093 1800 mg and 2400 mg.

Study 118: A double-blind, randomized, placebo-controlled, sequential multiple ascending dose study to investigate the safety and pharmacokinetics of eslicarbazepine in adult healthy volunteers.

Objectives:

- To determine a maximum tolerated supratherapeutic dose of eslicarbazepine acetate that could be safely administered in the planned thorough QT trial.

The study design is as follows:

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Study Design	Single centre, Phase I, double-blind, randomized, placebo-controlled, sequential study
Study Population	N=16 Healthy subjects (12 for PK) Age: 20-44 years (mean 33.7 years) Gender: 8 males and 8 females Weight: 61-85 kg (mean 70 kg) Race: 13 White, 3 Black
Treatment Group	<table><tr><th>Cohort</th><th>Planned Dose</th><th>Actual Dose</th></tr><tr><td>1</td><td>eslicarbazepine acetate 3600 mg (or matching placebo) once daily × 5 days</td><td>eslicarbazepine acetate 3600 mg (or matching placebo) once daily × 2 days</td></tr><tr><td>2</td><td>eslicarbazepine acetate 4800 mg (or matching placebo) once daily × 5 days</td><td>eslicarbazepine acetate 3000 mg (or matching placebo) once daily × 2 days</td></tr><tr><td>3</td><td>eslicarbazepine acetate 6000 mg (or matching placebo) once daily × 5 days</td><td>Subjects not dosed, study stopped</td></tr><tr><td>4</td><td>eslicarbazepine acetate 7200 mg (or matching placebo) once daily × 5 days</td><td>Subjects not dosed, study stopped</td></tr></table> 600 mg (Batch 050059-L)
Dosage and Administration	Multiple units of 600 mg with 240 ml water, preferably at the same time of the Day. Diet: On Days 1 and 5, subjects were to fast from at least 10 hours prior to dosing until 4 hours following dosing. Fasting was not required on Days 2, 3 and 4, and subjects were to be given breakfast at approximately one hour following dosing on those days. Dosing was stopped after Day 2 in both cohorts.
Sampling: Blood	For plasma BIA 2-093 and metabolites: Plasma samples were obtained 30 minutes prior to dose administration (0 hours, pre-dose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose. Trough samples were collected prior to the scheduled dosing time on Days 3 and 4. On Day 5, samples were collected 30 minutes prior to the scheduled dose administration (0 hours, predose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post-dose.
Urine	For urine BIA 2-093 and metabolites: On Days 1 and 5 just prior to administration of the test medication (time 0) and during the intervals of 0-4, 4-8, 8-12, and 12-24 hours post-dose.
Feces	none

Analysis	Lower Limits of Quantitation Plasma Urine BIA 2-093 50 ng/ml 10 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml 10 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml 10 ng/ml Oxcarbazepine 50 ng/ml 10 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 50, 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 50, 140, 400 and 800 ng/ml for oxcarbazepine Inter-day precision: % CV: < 4.7 %for BIA 2-194 and BIA 2-195 <3.9% % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 97.4-102 % for BIA 2-194 and BIA 2-195, 94-110% for BIA 2-093 and oxcarbazepine. Urine: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 50, 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 50, 140, 400 and 800 ng/ml for oxcarbazepine Inter-day precision: % CV: < 4.5 %for BIA 2-194 and BIA 2-195 <3.9% % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 93.4-109 % for BIA 2-194 and BIA 2-195, 91-118% for BIA 2-093 and oxcarbazepine.
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, CL/F, Vd/F
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Sixteen subjects were enrolled, 8 each in Cohorts 1 and 2. None of the subjects completed the study as scheduled. Across all subjects, 6 subjects were withdrawn for adverse events and 10 were withdrawn at the sponsor's request. Among the 6 subjects who received 3600 mg eslicarbazepine acetate in Cohort 1, 3 subjects (50%) discontinued as a result of adverse events and 3 subjects (50%) were withdrawn at the sponsor's request when the stopping criteria were reached in Cohort 1. Two subjects who received placebo in Cohort 1 were also discontinued at the sponsor's request. In Cohort 2, 3 subjects (50%) who received 3000 mg eslicarbazepine acetate discontinued for adverse events. The remaining 3 subjects in Cohort 2 who received 3000 mg eslicarbazepine acetate and the 2 who received placebo were withdrawn when the sponsor discontinued dosing and stopped the study.

Safety was assessed for all 16 subjects who received study drug. Pharmacokinetics were analyzed for the 12 subjects who received eslicarbazepine acetate.

Pharmacokinetic Results:

In plasma:

Dosing in both cohorts was stopped after the administration of 2 doses. For this reason, multiple dose pharmacokinetics could not be assessed in this study. Results provided in this section describe the pharmacokinetic results determined during a 24-hour period following the first dose on Day 1 of the study.

The mean BIA 2-194 (S-licarbazepine), BIA 2-195 (R-licarbazepine), and oxcarbazepine plasma concentrations over the 24-hour collection interval are displayed for the 3000 mg and 3600 mg doses in Figure 1 through Figure 3, respectively. BIA 2-093 was detected in the plasma of only one subject in the 3600 mg dose group (Subject 103) at a single time point following dosing.

The mean plasma concentrations of BIA 2-194 and BIA 2-195 for the 3000 and 3600 mg is shown in the Figure below:

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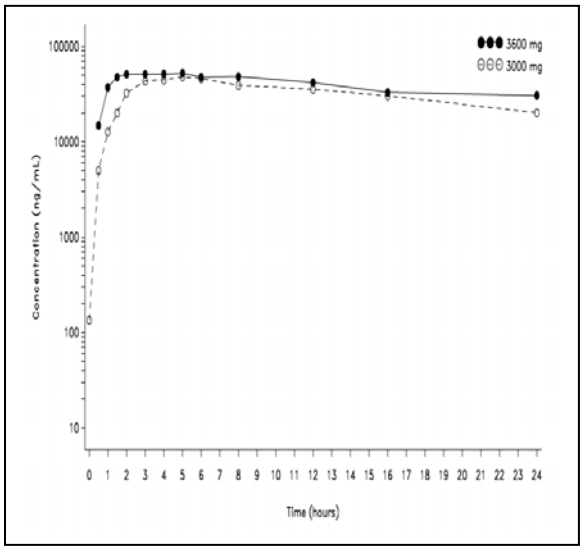
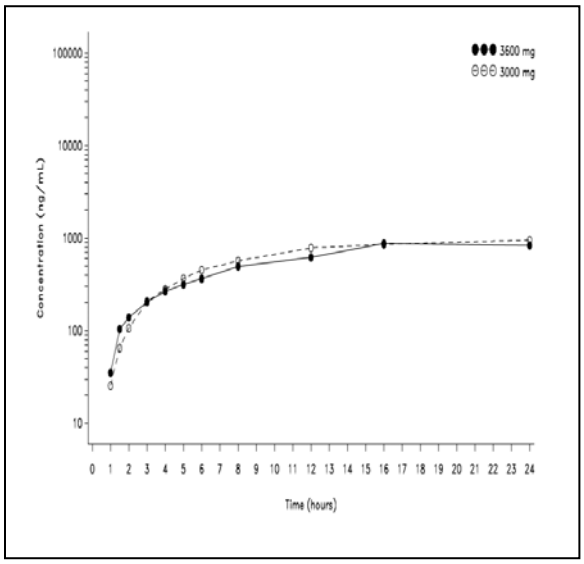


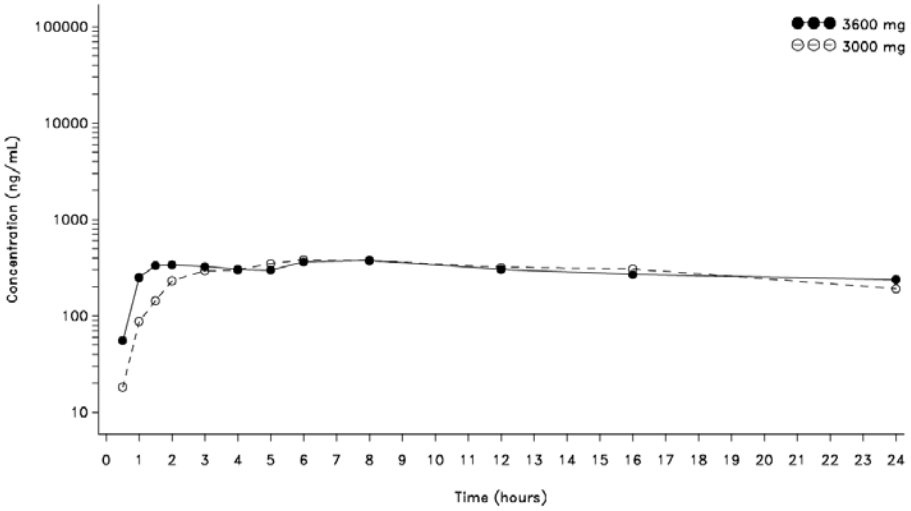
BIA 2-194



BIA 2-195

Following the single eslicarbazepine acetate dose on Day 1 (Figure 2), mean plasma concentration-time profiles of BIA 2-195 following the 3000 and 3600 mg doses appear similar through 24 hours after dosing. BIA 2-195 concentrations increased slowly after administration and appeared to reach maximum concentrations between 16 and 24 hours.

The mean oxcarbazepine plasma concentrations are shown in the following Figure:



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The mean Pharmacokinetic parameters is shown in the following Table:

Table. Summary of Eslicarbazepine Acetate Plasma Pharmacokinetic Results - Day 1

	Arithmetic Mean (SD)							
	3600 mg Eslicarbazepine Acetate				3000 mg Eslicarbazepine Acetate			
Parameter	BIA 2-194	BIA 2-195	Oxcarbazepine	BIA 2-093	BIA 2-194	BIA 2-195	Oxcarbazepine	BIA 2-093
C_{max} (µg/mL)	54.66 (11.492) n=6	0.89 (0.274) n=6	0.39 (0.101) n=6	0.01 (0.029) n=6	49.46 (10.642) n=6	0.96 (0.266) n=6	0.40 (0.085) n=6	0.00 n=6
T_{max} [a] (hour)	4.00 (1.50-5.00) n=6	20.00 (16.00-24.00) n=6	10.00 (6.00-16.00) n=6	0.50 (0.50) n=1	4.50 (3.00-5.00) n=6	24.00 (16.00-24.00) n=6	7.00 (6.00-8.00) n=6	n=0
$AUC_{0-\infty}$ (µg•hr/mL)	2237 (995.8) n=6	n=0	12.87 (7.066) n=3	n=0	1270 (255.1) n=6	n=0	12.29 (3.780) n=6	n=0
AUC_{0-t} (µg•hr/mL)	948 (265.0) n=6	14.10 (5.060) n=6	6.98 (2.201) n=6	0.00 (0.007) n=6	770 (108.8) n=6	15.48 (4.485) n=6	6.84 (0.743) n=6	0.00 n=6
AUC_{0-24} (µg•hr/mL)	948 (265.0) n=6	14.10 (5.060) n=6	6.98 (2.201) n=6	n=0	770 (108.8) n=6	15.48 (4.485) n=6	6.84 (0.743) n=6	n=0
K_{el} (hr^{-1})	0.0297 (0.01103) n=6	n=0	0.0327 (0.01915) n=3	n=0	0.0454 (0.01432) n=6	n=0	0.0446 (0.01676) n=6	n=0
t½ (hour)	27.37 (13.330) n=6	n=0	26.22 (13.426) n=3	n=0	16.88 (6.409) n=6	n=0	18.36 (9.509) n=6	n=0
Vd/F (L)	67.918 (25.1344) n=6	n=0	N/A	N/A	56.849 (14.0300) n=6	n=0	N/A	N/A
CL/F (L/hr)	2.042 (1.3170) n=6	n=0	N/A	N/A	2.425 (0.3775) n=6	n=0	N/A	N/A

[a] = median (range); N/A = not applicable

- BIA 2-194 (S-licarbazepine) was the predominant drug species detected in the plasma. As expected, mean BIA 2-194 Cmax and AUC0-t values were higher following the 3600 mg dose. Median Tmax values were similar at the two dosage levels and occurred at 4.00 and 4.50 hours following the 3600 mg and 3000 mg doses, respectively.
- The mean Cmax and AUC0-t values for BIA 2-195 (R-licarbazepine) and oxcarbazepine were similar between the two doses. Time to peak concentration for BIA 2-195 and oxcarbazepine were prolonged compared to BIA 2-194. Median Tmax values for BIA 2-195 were 24 hours and 20 hours and for oxcarbazepine were 7 hours and 10 hours for the 3000 and 3600 mg doses, respectively.

In Urine:

Urinary excretion for the 24 hour period is given in the Table below:

Table 7 Summary of Cumulative (0-24 Hours) Urinary Excretion and Renal Clearance of Eslicarbazepine and Metabolites on Day 1

		Urine Parameter (n) Mean		
Dose (mg)	**Analyte**	A_e (mg)	F_{E-UR} (%)	CL_R (mL/min)
3600				
	BIA 2-194	(6) 795.5209	(6) 25.75	(5) 15.04
	BIA 2-195	(6) 14.0611	(6) 0.46	(5) 20.13
	Oxcarbazepine	(6) 0.4480	(6) 0.01	(5) 1.34
	BIA 2-093	(6) 0.0266	(6) 0.00	-
3000				
	BIA 2-194	(6) 975.7252	(6) 37.90	(6) 20.89
	BIA 2-195	(6) 25.1302	(6) 0.98	(6) 26.34
	Oxcarbazepine	(6) 0.9340	(6) 0.04	(6) 2.27
	BIA 2-093	(6) 0.0122	(6) 0.00	-

A_e=Amount of drug excreted in urine; F_{E-UR}=Percentage of total dose excreted in the urine; CL_R=renal clearance

- Eslicarbazepine and metabolites were detected in the urine in the 24-hour period following a single dose on Day 1, primarily as the S-enantiomer of licarbazepine (BIA 2-194) which represented approximately 26% and 38% of the 3600 mg and 3000 mg administered doses, respectively.

- Urinary excretion of the R-licarbazepine (BIA 2-195) and the other metabolites represented a smaller fraction of the administered dose recovered in the urine. At the 3600 mg dosage level, the mean amount excreted in the urine as a percentage of the administered dose on Day 1 was 0.46%, 0.01%, and 0.00%, for BIA 2-195, oxcarbazepine, and BIA 2-093, respectively, while 0.98%, 0.04%, and 0.00% of the administered dose was excreted as BIA 2-195, oxcarbazepine, and BIA 2-093 in the 24-hour period following the 3000 mg dose on Day 1.

Overall Conclusions:

- BIA 2-194 was the predominant drug species detected in the plasma following administration of eslicarbazepine acetate.
- Other minor metabolites were BIA 2-195 and oxcarbazepine.

Study 115: Disposition of eslicarbazepine acetate and its metabolites S-licarbazepine and R-licarbazepine following oral administration in healthy volunteers

Eslicarbazepine acetate is an ester of S-licarbazepine (also called as eslicarbazepine). Following oral administration, eslicarbazepine acetate is rapidly and extensively metabolized to S-licarbazepine (eslicarbazepine, BIA 2-194), its major metabolite, and to R-licarbazepine (BIA 2-195) and oxcarbazepine, minor metabolites. The proportion of S-licarbazepine and R-licarbazepine following oral administration of eslicarbazepine acetate is 21:1; when oxcarbazepine is administered orally, the same metabolites (S-licarbazepine and R-licarbazepine) appear, but in a different proportion (4:1). This study aims to contribute for further clarification of the pharmacokinetics of eslicarbazepine acetate and its metabolites, following oral administration.

The study design is as follows:

Study Design	Single centre, open-label, randomized study in four parallel groups of healthy volunteers
Study Population	N= 32, 8 Healthy subjects per group Age: 19-45 years (mean 40 years) Gender: 8 males and 8 females Weight: 55-93 kg (mean 75 kg) Race: 31 White, 1 Black
Treatment Group	Group 1 = 900 mg of eslicarbazepine acetate (ESL, BIA 2-093); Group 2 = 450 mg of S-licarbazepine +450 mg of R-licarbazepine; Group 3 = 450 mg of S-licarbazepine; Group 4 = 450 mg of Rlicarbazepine. In each group, the study consisted of a single-dose period (Phase A) followed by a repeated dose period of 7 days of duration in which the investigational product was administered once daily (Phase B). The repeated-dose phase started 96 h post single-dose. Tablets containing 900 mg of eslicarbazepine acetate (batch number: 050071-L), capsules containing 225 mg of S-licarbazepine (batch number: 060064-L), and capsules containing 225 mg of R-licarbazepine (batch number: 060065-L). Oral route.
Dosage and Administration	With 240 ml water, preferably at the same time of the Day. Diet: On Day 1 and Day 11, subjects were requested to fast overnight for at least 8 hours before dosing and to remain fasted until 1 hour post-dose; then, a standard breakfast was served.
Sampling: Blood	For plasma BIA 2-093 and metabolites: Phase A: pre-dose (Day 1); and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose. Phase B: Days 6 to 10 inclusively: pre-dose. Day 11 (last dose): pre-dose; and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.

Urine	For urine BIA 2-093 and metabolites: On Days 1 and 5 just prior to administration of the test medication (time 0) and during the intervals of 0-4, 4-8, 8-12, and 12-24 hours post-dose.
Feces	none
Analysis	Lower Limits of Quantitation Plasma BIA 2-093 50 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml Oxcarbazepine 50 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 50, 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 50, 140, 400 and 800 ng/ml for oxcarbazepine Inter-day precision: % CV: < 5.6 %for BIA 2-194 and BIA 2-195 <3.8% % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 93-106 % for BIA 2-194 and BIA 2-195, 91-117% for BIA 2-093 and oxcarbazepine. Urine: none
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

In plasma:

The pharmacokinetic profiles in different groups are shown below:

Figure A. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following a single dose of 900 mg of BIA 2-093 in Group 1

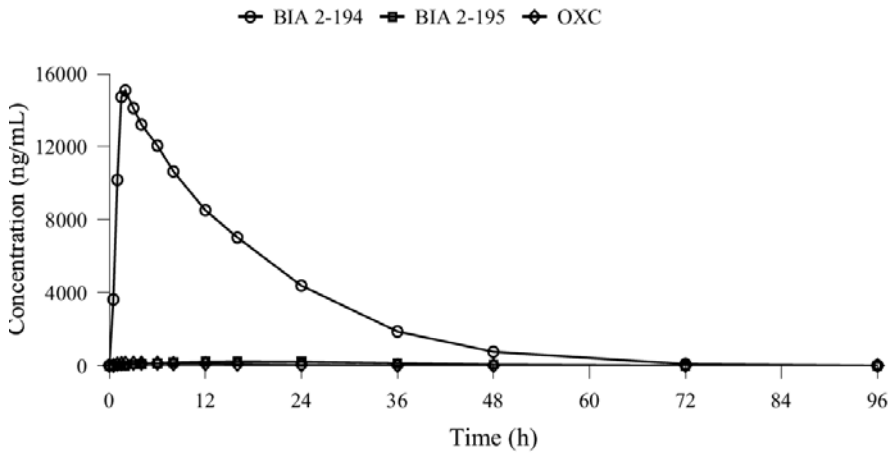


Figure B. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following a single dose of 450 mg of BIA 2-194 and 450 mg of BIA 2-195 in Group 2

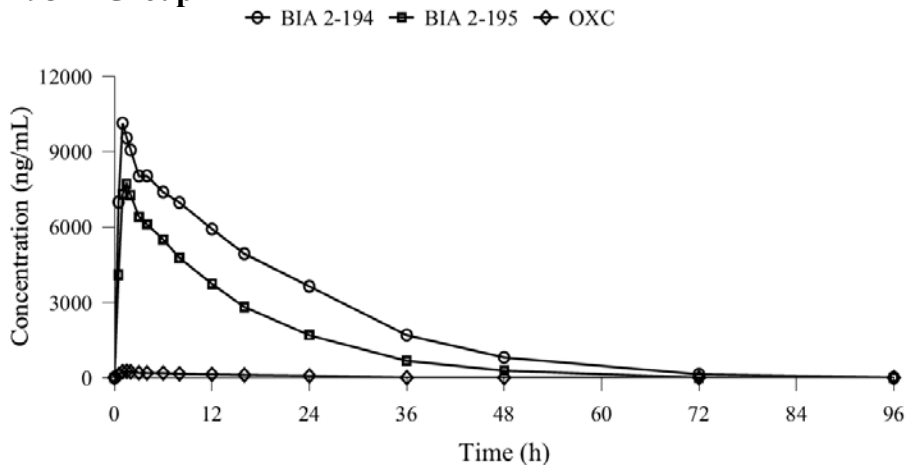


Figure C. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following a single dose of 450 mg of BIA 2-194 in Group 3

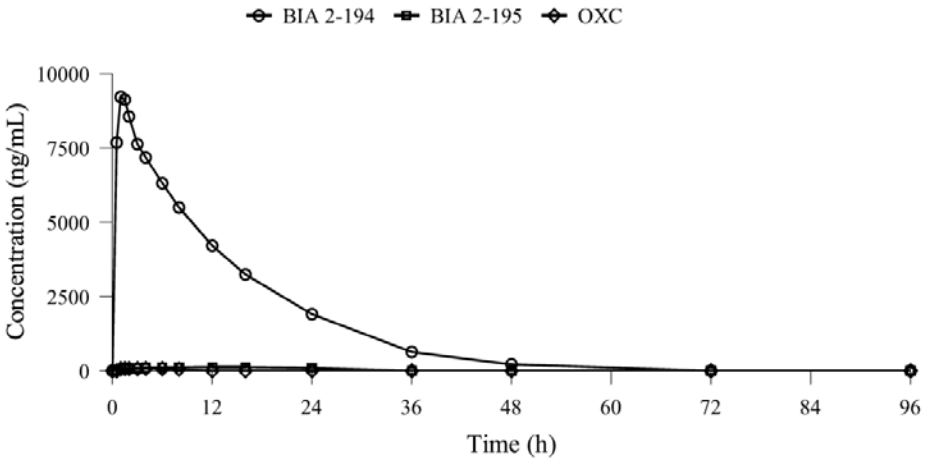
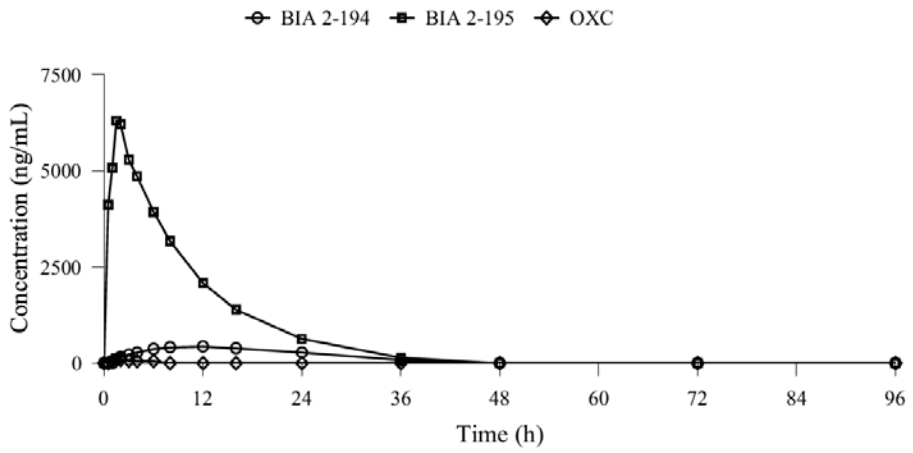


Figure D. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following a single dose of 450 mg of BIA 2-195 in Group 4



Similar profiles were also available after the last dose. Steady state was achieved. Mean PK parameters have been provided for BIA 2-093, BIA 2-194, BIA 2-195 and oxcarbazepine in each of the 4 groups after single dose and after 7 days of dosing.

The observations are as follows:

- In Group 1, following oral administration of single and repeated once-daily doses of 900 mg of ESL to healthy subjects, BIA 2-194 was the major circulating drug entity. BIA 2- 195 and Oxcarbazepine were minor metabolites, corresponding to approximately 4% and 1% of total drug exposure, as shown in the Table below.

Pharmacokinetic parameters of BIA 2-194, BIA 2-195, oxcarbazepine after a single 900 mg dose.

	C_{max} (ng/mL)	**T_{max}** (h)	**AUC_{τ}** (ng h/mL)	**$AUC_{0-\infty}$** (ng h/mL)	**$t_{1/2}$**(h)
BIA 2-194	16084 (19.8)	0.916 (1.75)	209441 (16.7)	275054 (17.2)	9 (1.75)
BIA 2-194	230 (29.7)	19 (21.8)	4018 (32)	9043 (24)	16.8 (27)
Oxcarb	138 (18.2)	3.94 (41)	2066 (28.5)	3344 (32.2)	14.8 (35.4)

Similar results were seen after multiple doses too.

- In Group 2, following oral administration of single and repeated once-daily doses of 450 mg of BIA 2-194 and 450 mg of BIA 2-195 to healthy subjects, BIA 2-194 was the major circulating drug entity. BIA 2-195 exposure was 65% and 48% of that to BIA 2-194 following single dose and following repeated doses,

respectively. Oxcarbazepine was a minor metabolite, corresponding to approximately 1% of total drug exposure (Table not shown, see EDR). These results showed that BIA 2-194 presents a better bioavailability than BIA 2-195, following oral administration.

- In Group 3, following oral administration of single and repeated once-daily doses of 450 mg of BIA 2-194 to healthy subjects, BIA 2-194 was the major circulating drug entity. BIA 2-195 and Oxcarbazepine were minor metabolites, corresponding to approximately 4% and 1% of total drug exposure (Table not shown, see EDR). These results are similar to those reported following oral administration of ESL in Group 1, and are consistent with the assumption that the first metabolic step following oral administration of ESL is its transformation to BIA 2-194.

- In Group 4, following oral administration of single and repeated once-daily doses of 450 mg of BIA 2-195 to healthy subjects, BIA 2-195 was the major circulating drug entity. BIA 2-194 exposure was 11% and 18% of that to BIA 2-195 following single dose and following repeated doses, respectively. Oxcarbazepine was a minor metabolite, corresponding to approximately 1% of total drug exposure (Table not shown, see EDR).

- Globally, it was apparent that BIA 2-194 is the predominating circulating entity following oral administration of ESL or oral administration of BIA 2-194. In both cases it represents approximately 95% of systemic drug exposure, and BIA 2-195 and Oxcarbazepine responsible for approximately 4% and 1%, respectively. Following oral administration of BIA 2-195, BIA 2-195 was the predominating circulating entity, but it was apparent a significant transformation into BIA 2-194, which corresponded to 11% and 18% of systemic exposure following single and repeated doses of 450 mg of BIA 2-195.

Overall Conclusions:

BIA 2-194 is the major circulating drug entity, BIA 2-195 and Oxcarbazepine are the minor metabolites.

PK COMPARISON TO TRILEPTAL:

Study 104: Tolerability and pharmacokinetics of a single 900 mg oral dose of BIA 2-093 and oxcarbazepine in healthy volunteers.

Objectives:

- To investigate the pharmacokinetics of BIA 2-093 and its metabolites and of Trileptal® and its metabolites following the administration of a single oral dose of 900 mg to healthy volunteers.
- To assess the tolerability of a 900 mg single dose of BIA 2-093 in comparison with that of a similar dose of Trileptal®.

The study design is as follows:

Study Design	Open-label, balanced randomized, 2-way crossover study of single oral 900 mg doses of BIA 2-093 and of Oxcarbazepine. The two study periods were to be separated by a washout period of 7 days or more.
Study Population	N=12 Healthy subjects Age: 20-45 years (mean 28 years) Gender: 6 males and 7 females Weight: 50.3-86.1 kg (mean 68.5 kg) Race: 12 White
Treatment Group	BIA 2-093 and Trileptal
Dosage and Administration	Subjects received single oral doses of BIA 2-093 or Trileptal®, administered in the form of tablets, given with 200 mL potable water. The dose level investigated was 900 mg for each compound. The dosing was to occur between 08:00 and 09:00, in the morning, following an overnight fasting of at least 8 hours. Dosing times were slightly staggered between subjects for practical reasons. Batch number BIA 2-093 300 mg tablets 20104 BIA 2-093 600 mg tablets 10575 Tolep® 300 mg tablets S48300A (Italian brand) Tolep® 600 mg tablets S29300A
Sampling: Blood	Blood samples for the assay of plasma BIA 2-093 and its metabolites (BIA 2-194, BIA 2- 195 and Oxcarbazepine) and Trileptal® and its metabolites BIA 2-194 and BIA 2-195 (which mixture is commonly referred as MHD in the literature) were to be taken at the following times: pre-dose, ½, 1, 1½, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours postdose.
Urine	none.
Feces	none
Analysis	Lower Limits of Quantitation Plasma

	BIA 2-093 50 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml Oxcarbazepine 50 ng/ml <u>Plasma:</u> Method: LC/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 10000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 100, 4000, 8000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 100, 040, 400 and 800 and 2000 ng/ml for oxcarbazepine Inter-day precision: % CV: < 8 %for BIA 2-194 and BIA 2-195 <6.9% % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 102 -110% for BIA 2-194 and BIA 2-195, 99-101% for BIA 2-093 and oxcarbazepine.
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

<u>Pharmacokinetic Results:</u>

The mean plasma concentrations of BIA 2-194, BIA 2-195 and oxcarabazepine, following administration of 900 mg BIA 2-093 and Trileptal is shown in the following Figures:

Figure A. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following oral administration of 900 mg of BIA 2-093

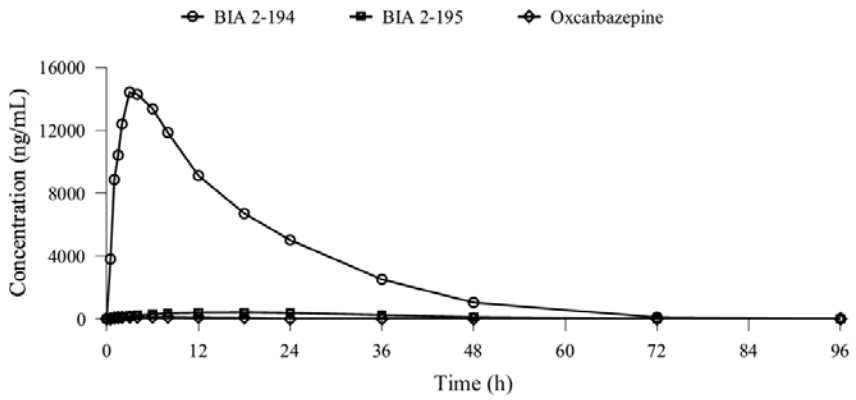
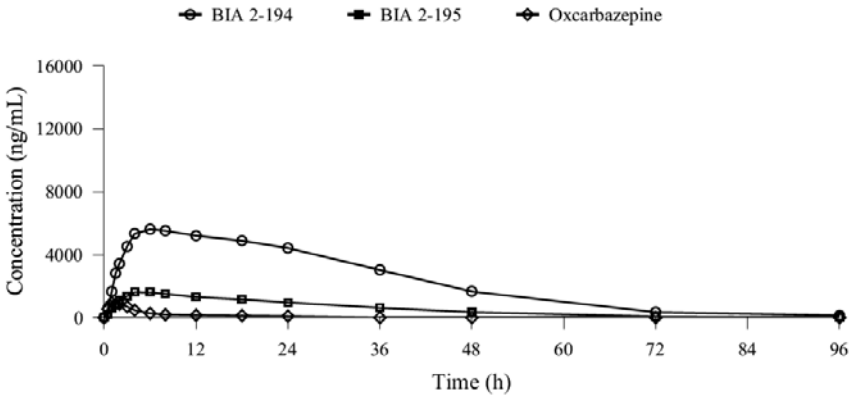


Figure B. Mean plasma BIA 2-194, BIA 2-195 and Oxcarbazepine concentration-time profiles following oral administration of 900 mg of Trileptal®



Following a single dose of 900 mg of BIA 2-093

Plasma concentrations of BIA 2-093 after a single dose of 900 mg of BIA 2-093 were systematically found to be below the limit of quantification (50 ng/mL). Thus, individual and mean kinetic parameters for BIA 2-093 could not be determined. The pharmacokinetic parameters of BIA 2-093 metabolites are summarized in the following Table:

Table D. Pharmacokinetic parameters of BIA 2-093 metabolites following a single oral dose of 900 mg of BIA 2-093 (n=12 unless otherwise specified)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
BIA 2-194	15753 (3781)	3 (1-6)	299065 (65077)	301693 (63885)	0.0866 (0.0140)	8.22 (1.50)
BIA 2-195	428 (88.6)	15 (8-18)	13877 (2867)	16779 (3597)	0.0470 (0.00936)	15.3 (2.86)
Oxcarbazepine	140 (37.7)	6 (1.5-18)	1821 (693)	3443* (2028)	0.0351* (0.0196)	15.6* (11.2)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
t_{max} values are median with range values in parentheses.
*n=10 (terminal monoexponential phase could not be unambiguously identified for subjects #002 and #007).

Following a single dose of 900 mg of Trileptal® the pharmacokinetic parameters of Trileptal® and its metabolites are summarized in Table E.

Table E. Pharmacokinetic parameters of Oxcarbazepine and its metabolites following a single oral dose of 900 mg of Trileptal® (n=12)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
BIA 2-194	5978 (1136)	6 (1.5-24)	214433 (45162)	220532 (46090)	0.0590 (0.0174)	13.1 (5.07)
BIA 2-195	1708 (751)	6 (2-18)	49124 (18926)	52648 (19925)	0.0531 (0.0139)	13.9 (3.65)
Oxcarbazepine	1268 (656)	2 (1-4)	6549 (3927)	8936 (4838)	0.0534 (0.0324)	19.0 (13.7)

Comparison of systemic exposure
The main pharmacokinetic parameters of eslicarbazepine and (R)-licarbazepine following a single 900 mg oral dose of SEP-0002093 and oxcarbazepine are presented in Table F

Table F: Mean (SD) pharmacokinetic parameters of eslicarbazepine and (R)-licarbazepine following a single oral dose of 900 mg of SEP-0002093 or Oxcarbazepine

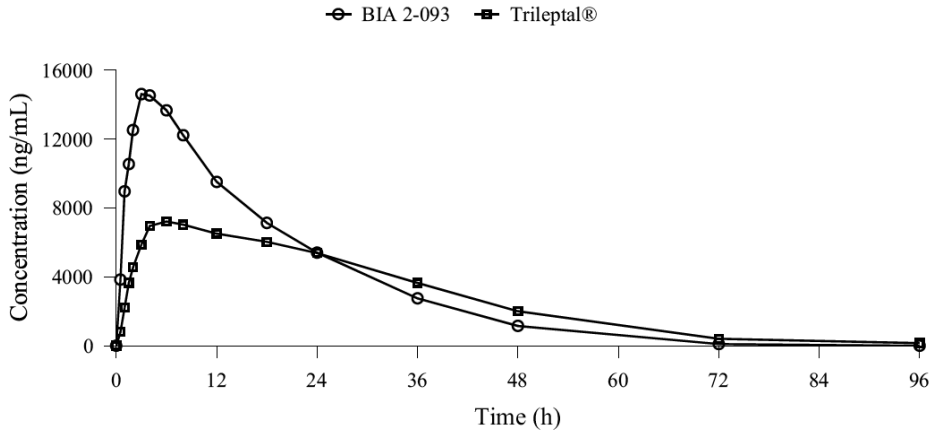
	900 mg SEP-0002093, single-dose, p.o.		**900 mg Oxcarbazepine, single-dose, p.o.**	
	C_{max} (µg/mL)	**$AUC_{0-\infty}$ (µg·h/mL)**	**C_{max} (µg/mL)**	**$AUC_{0-\infty}$ (µg·h/mL)**
Eslicarbazepine	15.8 (3.8)	301.7 (63.9)	6.0 (1.1)	220.5 (46.1)
(R)-Licarbazepine	0.4 (0.09)	16.8 (3.6)	1.7 (0.8)	52.6 (19.9)

The percentage of total systemic exposure when given BIA 2-193 or Trileptal® is given in the following Table:
Table G. Percentage of total systemic exposure (as assessed by AUC0-t)

	BIA 2-093 (900 mg)	**Trileptal (900 mg)**
BIA 2-194	**95.04%**	**80.08%**
BIA 2-195	**4.41%**	**17.7%**
Oxcarabazepine	**0.55**	**2.22%**

For allowing a comparison of global systemic exposure following administration of BIA 2-093 and Trileptal®, a combined parameter was derived: [BIA 2-194 plus BIA 2-195]. Since BIA 2-093 is chemically related with Oxcarbazepine and its 10-monohydroxy (MHD, Licarbazepine) metabolite is a mixture of BIA 2-194 (SLicarbazepine) and BIA 2-195 (R-Licarbazepine), the comparison of their PK profiles of this was conducted. Mean concentration versus time profiles of [BIA 2-194 plus BIA 2-195] following administration of BIA 2-093 and Trileptal® are illustrated in Figure C.

Figure C. Mean plasma [BIA 2-194 plus BIA 2-195] concentration-time profiles following oral administration of 900 mg of BIA 2-093 or Trileptal®



The pharmacokinetic parameters of [BIA 2-194 plus BIA 2-195] following administration of BIA 2-093 and Trileptal® are presented in Table H.

Table H. Pharmacokinetic parameters of [BIA 2-194 plus BIA 2-195] following a single oral dose of 900 mg of BIA 2-093 or Trileptal® (n=12)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
BIA 2-093	15929 (3787)	3 (1-6)	314272 (67824)	317020 (66409)	0.0888 (0.0150)	8.05 (1.61)
Trileptal®	7640 (1680)	6 (1.5-24)	264890 (59383)	271843 (62343)	0.0617 (0.0178)	12.4 (4.70)

Following administration of a single dose of 900 mg of BIA 2-093, Cmax of [BIA 2-194 plus BIA 2-195] was reached (tmax) between 1 and 6 h post-dose (median of 3 h), after which it declined with a t1/2 of 8.05 h. Following administration of a single dose of 900 mg of Trileptal®, tmax of [BIA 2-194 plus BIA 2-195] occurred between 1.5 and 24 h post-dose (median of 6 h) and t1/2 was 12.4 h. Ratios between BIA 2-093 metabolites and Trileptal® metabolites were calculated for Cmax and AUC0-t and summarized below in Table H.

Table H. Ratios between Cmax and AUC0-t of [BIA 2-194 plus BIA 2-195] obtained following a single oral dose of 900 mg of BIA 2-093 or Trileptal® (n=12)

	C_{max} [BIA 2-194 + BIA 2-195] (ng/mL)	AUC_{0-t} [total] (ng.h/mL)	AUC_{0-t} [BIA 2-194 + BIA 2-195] (ng.h/mL)
BIA 2-093 (A)	15505	308500	308207
Trileptal® (B)	7471	261970	258493
Ratio A/B	2.08	1.18	1.19

Results are expressed as geometric means.

AUC_{0-t} was used instead of $AUC_{0-\infty}$ because terminal monoexponential phase could not unambiguously identified in two subjects (#002 and #007).

AUC_{0-t} [total] was obtained by the sum of Oxcarbazepine, BIA 2-194 and BIA 2-195 concentrations at each time-point.

AUC_{0-t} [BIA 2-194 plus BIA 2-195] was obtained by the sum of BIA 2-194 and BIA 2-195 concentrations at each time-point.

In molar terms, 900 mg of SEP-0002093 represents a 15% lower dose than 900 mg of oxcarbazepine (the molecular weight of SEP-0002093 is 296 and that of oxcarbazepine is 252, 900 mg of SEP-0002093 (3,037 µmol) or 900 mg of oxcarbazepine (3,568 µmol)). Nevertheless, the extent of systemic exposure expressed as the total AUC of the two active entities (eslicarbazepine and (R)-licarbazepine) was 19% higher following oral administration of SEP-0002093 (900 mg) than following administration of oxcarbazepine (900 mg). Altogether, the results suggest that SEP-0002093 has a higher oral bioavailability than oxcarbazepine.

Safety:

The most common adverse event (occurring in 2 or more subjects) considered possibly

related to treatment was dizziness, reported by 3 subjects (23.1%): 2 cases with BIA 2-093 and one case with Trileptal®. Skin and subcutaneous tissue disorder and nodule subcutaneous was seen in one case with Trileptal® and none with BIA 2-093.

Overall Conclusions:

Following a single oral dose of 900 mg, BIA 2-093 appeared to be rapidly and extensively metabolized to S-Licarbazepine (BIA 2-194). The S-enantiomer was responsible for more than 95% of systemic total drug exposure. The R-enantiomer (R-Licarbazepine, BIA 2- 195) and Oxcarbazepine were minor metabolites. Parent drug (BIA 2-093) was not detectable in plasma.

Following a single oral dose of 900 mg of Trileptal®, Oxcarbazepine appeared to be metabolized to S-Licarbazepine and R-Licarbazepine (BIA 2-194 and BIA 2-195, respectively) in the ratio of approximately 4:1.

The comparison of the kinetic profiles following administration of a single dose of 900 mg of BIA 2-093 and a similar dose of Trileptal® suggests that BIA 2-093 can provide a higher systemic drug exposure: Cmax ratio of [BIA 2-194 plus BIA 2-195] was 2.08 and AUC0-t ratio was 1.19.

Study 110: Steady State pharmacokinetics of BIA 2-093 and oxcarbazepine in healthy volunteers.

Objectives:

- To investigate the steady-state pharmacokinetics of once-daily and twice-daily regimens of BIA 2-093 and twice-daily regimen of Trileptal® in healthy subjects.
- To assess the tolerability of once-daily and twice-daily regimens of BIA 2-093 and twice daily regimen of Trileptal® in healthy subjects.

The study design is as follows:

Study Design	This was a single-centre, open-label, randomized and three-way crossover study in 12 healthy volunteers. The study consisted of three 8-day treatment periods separated by washout periods of 10-15 days
Study Population	N=12 Healthy subjects (10 completed, 11 with PK) Age: 21-36 years (mean 29 years) Gender: 6 males and 6 females Weight: 51.8-96.9 kg (mean 68.5 kg) Race: 12 White
Treatment Group	BIA 2-093: 900 mg OD BIA 2-093: 450 mg BID Trileptal; 450 mg BID
Dosage and Administration	On Day 1, subjects were to attend the UFH early in the morning and remained in the UFH until 3 h post first dose, for assessing reaction to the first dose. Then, they were to leave and to return at the morning (and evening, in the periods of bid regimen) for the investigational product administration and other study procedures. On the evening of Day 7, subjects were to be admitted to the UFH; on the morning of Day 8, subjects were to receive the last dose of investigational product and remained in the UFH until 24 h post- dose; then, they would leave and return 36 h, 48 h, 72 h and 96 h post last dose for blood sampling and other study procedures. After the 96 h evaluation, the subjects were discharged. Batch number BIA 2-093 450 mg tablets 030144-L Trileptal® 150 mg tablets SA2500 Trileptal® 300 mg tablets SO5500
Sampling: Blood	Blood samples for the assay of plasma BIA 2-093 and its metabolites (BIA 2-194, BIA 2- 195 and Oxcarbazepine) and Trileptal® and its metabolites BIA 2-194 and BIA 2-195 (which mixture is commonly referred as MHD in the literature) were to be taken at the following times in each treatment period: Day 1 to Day 7: pre-morning dose; Day 8: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 h post-dose.
Urine	none.
Feces	none
Analysis	Lower Limits of Quantitation Plasma BIA 2-093 50 ng/ml

	BIA 2-194 (S-licarbazepine) 100 ng/ml BIA 2-195 (R-licarbazepine) 100 ng/ml Oxcarbazepine 50 ng/ml <u>Plasma:</u> Method: HPLC/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 100 – 10000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 100, 4000, 8000, 20000* (with dilution) ng/ml for BIA 2-194 and BIA 2-195; 100, 040, 400 and 800 and 2000* (with dilution) ng/ml for oxcarbazepine Inter-day precision: % CV: < 9.24 %for BIA 2-194 and BIA 2-195 <9.93 % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 93-100% for BIA 2-194 and BIA 2-195, 93-99% for BIA 2-093 and oxcarbazepine.
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

In total, 12 subjects entered the study. Ten subjects completed the study through to the final follow-up visit. One subject (#001) was removed from the study at Day 2 of Period 2 (BIA 2-093 450 mg bid), at the discretion of the Principal Investigator, due to a diffuse macular rash; this patient has valid pharmacokinetic data for the BIA 2-093 900 mg od period (Period 1), but did not participate in the pharmacokinetic analyses corresponding to the BIA 2-093 450 mg bid (Period 2) and Trileptal® 450 mg bid (Period 3). The plasma concentrations of BIA 2-194 in this subject was not higher than the rest of the subjects at all time points. One subject (#011) was removed from the study after completion of Period 2 (Trileptal® 450 mg bid), at the discretion of the Principal Investigator, due to increase of transaminases (aminotransferases), that had also occurred during Period 1 (BIA 2-093 450 mg bid); this patient has valid pharmacokinetic data for the BIA 2-093 450 mg bid period (Period 1) and Trileptal® 450 mg bid (Period 2), but did not participate in the pharmacokinetic analysis corresponding to the BIA 2-093 900 mg od (Period 3). Thus, data from 11 subjects were available for pharmacokinetic analysis for each treatment.

BIA 2-093 was extensively metabolized to BIA 2-194; BIA 2-195 and OXC were minor metabolites. Trileptal® was also metabolized to BIA 2-194 and BIA 2-195, which enantiomeric mixture is commonly referred in the literature as “MHD”.

Following the last dose of an 8-day once-daily 900 mg dose of BIA 2-093, the pharmacokinetic parameters (mean and SD) of BIA 2-194, BIA 2-195 and OXC were as follows:

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	Fluctuaction (%)
BIA 2-194	22210 (7257)	3.0 (1.5-4.0)	381601 (95368)	294019 (58364)	389344 (97383)	9.12 (1.19)	131 (33.4)
BIA 2-195	685 (188)	12.0 (1.5-18.0)	20164 (6790)	13654 (3209)	24663 (6984)	15.0 (3.65)	41.1 (15.4)
OXC	208 (53.2)	6.0 (1.5-12.0)	3238 (1033)	3114 (717)	4551 (1127)	13.2 (4.43)	128 (42.2)

The pharmacokinetic parameters of BIA 2-194, BIA 2-195 and OXC following the last dose of an 8-day twice-daily 450 mg dose of BIA 2-093 were as follows:

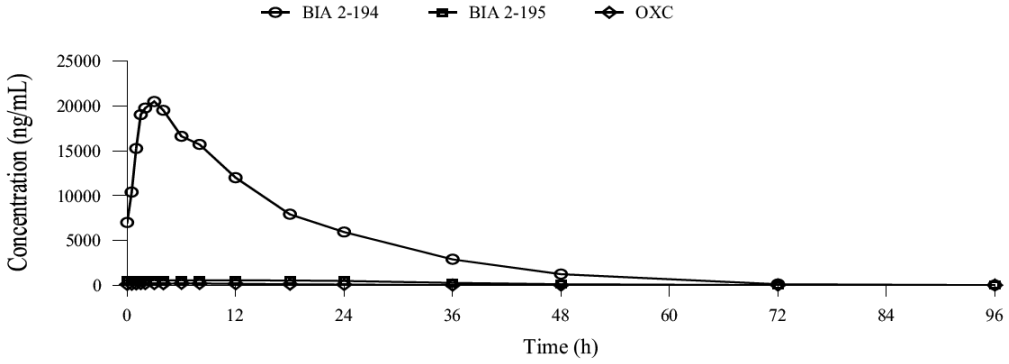
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	Fluctuaction (%)
BIA 2-194	16667 (3981)	2.0 (1.0-2.0)	283014 (74203)	142080 (25933)	289792 (74346)	9.17 (1.49)	69.7 (20.4)
BIA 2-195	702 (182)	6.0 (1.5-12.0)	19091 (6042)	7586 (2080)	23074 (7206)	14.5 (4.02)	28.6 (7.76)
OXC	182 (47.2)	3.0 (1.0-12.0)	2699 (909)	1672 (471)	3870 (1056)	11.9 (2.88)	69.4 (27.0)

Following the last dose of an 8-day twice-daily 450 mg dose of Trileptal®, the pharmacokinetic parameters of BIA 2-194, BIA 2-195 and OXC were as follows:

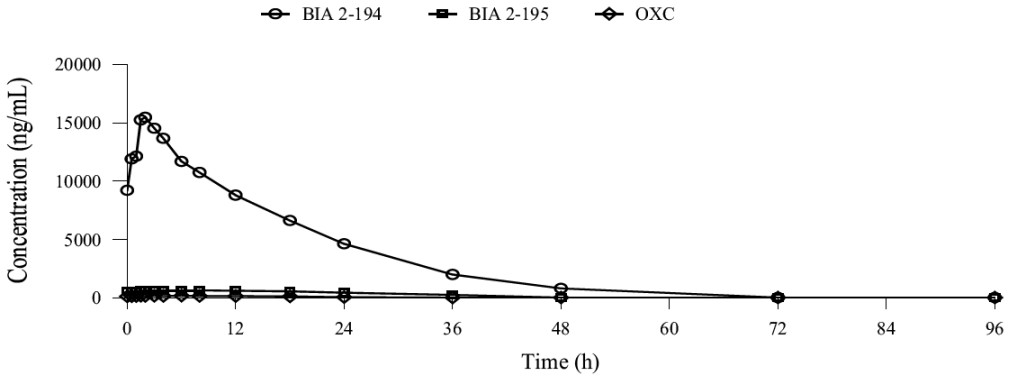
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	Fluctuaction (%)
BIA 2-194	12195 (2053)	3.0 (1.5-6.0)	268376 (43294)	123125 (16606)	273012 (43723)	9.24 (3.25)	39.4 (9.03)
BIA 2-195	2481 (362)	3.0 (1.5-8.0)	48841 (9041)	23965 (2953)	52807 (9729)	11.0 (2.05)	50.4 (17.7)
OXC	1080 (548)	1.0 (0.5-3.0)	5196 (1472)	3984 (1119)	6129 (1459)	10.1 (3.41)	278 (77.0)

The pharmacokinetic profiles after the three treatments are given below:

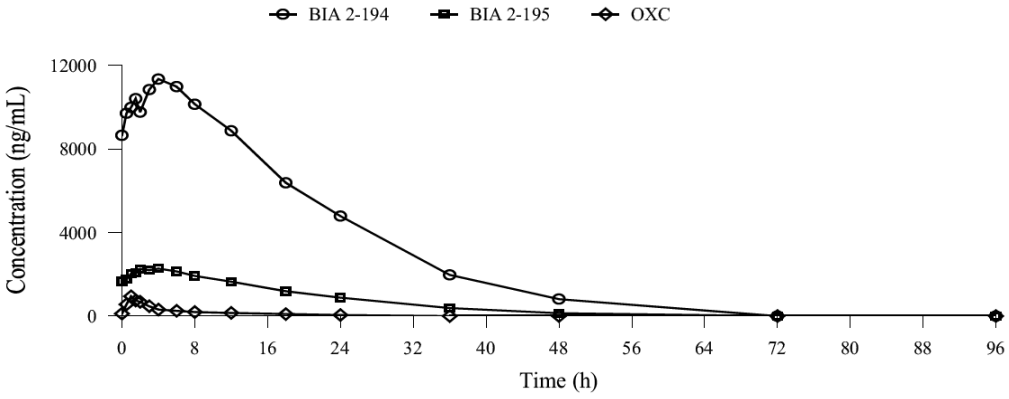
Plasma concentration versus time profiles of BIA 2-194, BIA 2-195 and OXC following the last dose of an 8-day once-daily 900 mg dose of BIA 2-093 (n=11)



Plasma concentration versus time profiles of BIA 2-194, BIA 2-195 and OXC following the last dose of an 8-day twice-daily 450 mg dose of BIA 2-093 (n=11)



Plasma concentration versus time profiles of BIA 2-194, BIA 2-195 and OXC following the last dose of an 8-day twice-daily 450 mg dose of Trileptal® (n=11)



Comparison of systemic exposure between BIA 2-093 once-daily, BIA 2-093 twice daily and Trileptal® twice-daily treatments

The rate and extent of systemic exposure to the active moieties following the different treatment regimens studied in this study were compared by calculating the ratios of C_{max}

and AUC geometric means of BIA 2-194 plus BIA 2-195 plus OXC [BIA 2-194 + BIA 2-195 + OXC] obtained following the last dose of each treatment period.

The following Table presents the ratios between the C_{max} of the sum of the three active moieties (BIA 2-194, BIA 2-195 and OXC) obtained following the last dose of the three treatment alternatives studied.

Table. Ratios between the geometric means of [BIA 2-194 + BIA 2-195 + OXC] Cmax following the last dose of an 8-day regimen with three treatments

	[BIA 2-194 + BIA 2-195 + OXC] $\mathbf{C_{max}}$
BIA 2-093 900 mg od (A)	24966 ng/mL
BIA 2-093 450 mg bid (B)	17089 ng/mL
Trileptal® 450 mg bid (C)	15490 ng/mL
Ratio A/B	1.29
Ratio A/C	1.42
Ratio B/C	1.10

The ratios between the $AUC_{0-\tau}$ of the three active moieties (BIA 2-194, BIA 2-195 and OXC) and of their sum obtained following the last dose of the three treatment alternatives was studied. In order to allow to compare the extent of systemic exposure to the different active moieties during a 24-h period (dosing interval when a once-daily dosing is used), the $AUC_{0-\tau}$ (AUC_{0-12h}) of BIA 2-194 plus BIA 2-195 plus OXC following the last dose of the 8-day twice-daily regimen with 450 mg of BIA 2-093 or Trileptal® was doubled.

Ratio between the BIA 2-194, BIA 2-195 and OXC $AUC_{0-\tau}$ (AUC_{0-24h})

	OXC	BIA 2-194	BIA 2-195	Sum
BIA 2-093 900 mg od (A)	3030 ng.h/mL (0.99%)	288280 ng.h/mL (94.64%)	13299 ng.h/mL (4.37%)	304609 ng.h/mL (100%)
BIA 2-093 450 mg bid (B)	3230 ng.h/mL (1.08%)	280002 ng.h/mL (94.00%)	14638 ng.h/mL (4.92%)	297870 ng.h/mL (100%)
Ratio A/B	0.94	1.03	0.91	1.02

Ratio between the BIA 2-194, BIA 2-195 and OXC $AUC_{0-\tau}$ (AUC_{0-24h})

	OXC	BIA 2-194	BIA 2-195	Sum
BIA 2-093 900 mg od (A)	3030 ng.h/mL (0.99%)	288280 ng.h/mL (94.64%)	13299 ng.h/mL (4.37%)	304609 ng.h/mL (100%)
Trileptal® 450 mg bid (B)	7694 ng.h/mL (2.57%)	244452 ng.h/mL (81.55%)	47604 ng.h/mL (15.88%)	299750 ng.h/mL (100%)
Ratio A/B	0.39	1.18	0.28	1.02

Ratio between the BIA 2-194, BIA 2-195 and OXC $AUC_{0-\tau}$ (AUC_{0-24h})

	OXC	BIA 2-194	BIA 2-195	Sum
BIA 2-093 450 mg bid (A)	1615 ng.h/mL (1.08%)	140001 ng.h/mL (94.00%)	7319 ng.h/mL (4.92%)	148935 ng.h/mL (100%)
Trileptal® 450 mg bid (B)	3847 ng.h/mL (2.57%)	122226 ng.h/mL (81.55%)	23802 ng.h/mL (15.88%)	149875 ng.h/mL (100%)
Ratio A/B	0.42	1.15	0.31	0.99

Overall Conclusions:

- Following the last dose of an 8-day oral administration treatment period with BIA 2-093 900 mg once-daily, BIA 2-093 450 mg twice-daily and Trileptal® 450 mg twice-daily, the active moieties found in plasma were S-licarbazepine (BIA 2-194), R-licarbazepine (BIA 2-195) and oxcarbazepine. However, proportions of these metabolites differed substantially between BIA 2-093 and Trileptal®.
- Following administration of BIA 2-093 900 mg once-daily and 450 mg twice-daily, Slicarbazepine was responsible for approximately 95% of systemic total drug exposure, as assessed by AUC. Parent drug (BIA 2-093) was not detectable in plasma. R-Licarbazepine and oxcarbazepine were minor metabolites, representing respectively about 1% and 4% of systemic exposure. Plasma C_{max} of the sum of the active moieties (S-licarbazepine + Rlicarbazepine + oxcarbazepine) was 29% higher following administration of BIA 2-093 900 mg once-daily in comparison with BIA 2-093 450 mg twice-daily. The extent of exposure to active moieties (as assessed by AUC) during 24 hours while on a BIA 2-093 900 mg once-daily regimen was identical to that induced by a BIA 2-093 450 mg twice daily regimen (ratio BIA 2-093 900 mg / BIA 2-093 450 mg AUC_{0-24} / $2xAUC_{0-12}$ = 1.02).
- Following administration of BIA 2-093 900 mg once-daily and Trileptal® 450 mg twice-daily, the ratio for ratio BIA 2-093 900 mg / Trileptal® 450 mg AUC_{0-24} / $2xAUC_{0-12}$ = 1.02 and the Cmax was 42% higher.

- Following administration of Trileptal® 450 mg twice-daily, S-licarbazepine and Rlicarbazepine were responsible for respectively 82% and 16% of systemic total drug exposure, as assessed by AUC. Oxcarbazepine accounted for approximately 3%. Plasma C_{max} of the sum of the active moieties (S-licarbazepine + R-licarbazepine + oxcarbazepine) was 10% higher following administration of BIA 2-093 450 mg twice-daily in comparison with Trileptal® 450 mg twice-daily. The extent of exposure to active moieties (as assessed by AUC) during 24 hours while on a BIA 2-093 450 mg twice-daily regimen was identical to that induced by a Trileptal® 450 mg twice-daily regimen (ratio BIA 2-093 / Trileptal® AUC_{0-12} / AUC_{0-12} = 0.99).

PK in PATIENTS:

BIA-2093-301 PK Sub-study: Pharmacokinetics of eslicarbazepine acetate (ESL, with development code BIA 2-093) in a subgroup of patients who were participating in an open-label extension (Part III) of a phase III study of ESL as adjunctive therapy for refractory partial seizures

Study Design:

Part I of this clinical study was performed as a multicentre, double-blind, randomized, placebo-controlled, parallel-group, phase III therapeutic confirmatory study. Duration of Part I was 26 weeks. During a single-blind 8-week baseline period all patients received placebo; at the end of this period patients were randomly assigned to one of the four treatment groups: ESL 1200 mg once daily, ESL 800 mg once daily, ESL 400 mg once daily, and placebo once daily. The baseline period was followed by a double-blind 2-week titration period, a 12-week maintenance period and a 4-week tapering-off period.

Patients who completed the 12-week maintenance and 4-week tapering-off periods of Part I could enter a 1-year open-label extension (Part II). Patients who completed the Part II could enter an additional 1-year open-label extension (Part III). During the open-label extensions, the investigator was free to titrate the ESL dose according to therapeutic response, at 400 mg intervals, in the dose range 400 mg to 1200 mg, once-daily.

PK Sub-Study design:
In one of the visits of Part III, blood samples for the determination of plasma concentrations of ESL and metabolites were taken at the following time-points in relation to dosing: pre-dose, and 1h, 2h, 3h, 4h, 6h, 8h, and 12h post-dose. For the 24 hour value, the plasma concentration at pre-dose was carried forward. All Phase III studies were limited to sparse sampling, hence PK was characterized in this substudy.

Number of patients analyzed: 51 patients, 23 females and 28 males with a mean (SD) age of: 41 (11.5) years (Median: 40 years, Min-Max: 20-64 years), all Caucasians

Test product, dose and mode of administration, batch number:
ESL was supplied as scored 800 mg tablets (batches numbers: 050052-L, 050053-L and 060179- L); 400 mg, 800 mg or 1200 mg once-daily administration, by oral route.

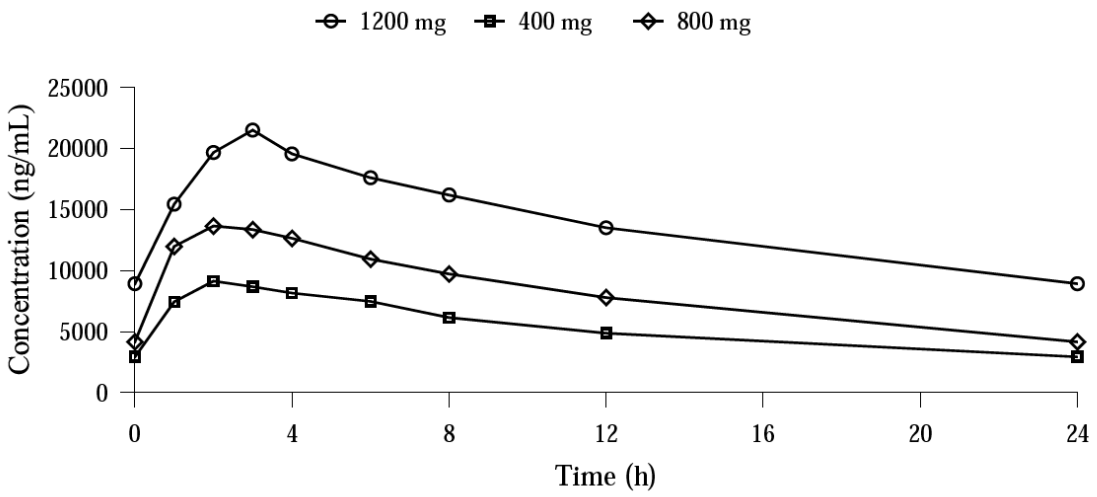
Concomitant Medications:

ATC Therapeutic Subgroup (2nd level)/ Generic name	Total N (%)
Total population	51 (100%)
Taking 1 AED	21 (41.2%)
Taking 2 AED	29 (56.9%)
ANTIEPILEPTICS	
Carbamazepine	34 (66.7%)
Valproic acid	19 (37.3%)
Lamotrigine	8 (15.7%)
Topiramate	5 (9.8%)
Levetiracetam	5 (9.8%)
Phenobarbital	4 (7.8%)
Clobazam	1 (2.0%)
Clonazepam	1 (2.0%)
Gabapentin	1 (2.0%)
Phenytoin	1 (2.0%)

Results:
ESL (parent drug) was rapidly and extensively metabolized to eslicarbazepine, the main metabolite. Pharmacokinetic parameters of ESL could not be calculated because the plasma concentrations were systematically below the limit of quantification of the assay (50 ng/mL). R-licarbazepine and OXC were minor metabolites.

Mean concentration-time profiles for eslicarbazepine following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD are displayed in the following Figure:

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



The mean pharmacokinetic parameters of eslicarbazepine, R-licarbazepine and OXC following oral administration of ESL 400 mg, 800 mg, and 1200 mg QD were as follows:

	ESL dose	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng.h/mL)	$t_{1/2}$ (h)
Eslicarbazepine (BIA 2-194)	400 mg (n=7)	9673 (5142)	2.0 (1.0-6.0)	132514 (89477)	12.8 (5.1)
	800 mg (n=26)	15462 (5000)	2.0 (1.0-6.0)	205359 (74584)	13.5 (6.1)
	1200 mg (n=18)	22957 (5263)	2.5 (1.0-6.0)	336147 (81654)	20.2 (10.9)
R-licarbazepine (BIA 2-195)	400 mg (n=7)	811 (223)	6.0 (6.0-12.0)	15650 (5840)	27.9 (13.7)
	800 mg (n=26)	949 (458)	8.0 (1.0-12.0)	18929 (9630)	25.3 (18.2)
	1200 mg (n=18)	1553 (409)	6.0 (2.0-12.0)	32120 (8304)	61.2 (58.7)
OXC	400 mg (n=7)	168 (67.6)	3.0 (1.0-6.0)	1935 (1271)	11.5 (1.9)
	800 mg (n=26)	232 (84.7)	3.0 (1.0-12.0)	2921 (1103)	12.0 (5.0)
	1200 mg (n=18)	385 (151)	3.0 (1.0-6.0)	5076 (1691)	14.3 (5.8)

Results expressed as arithmetic means with the corresponding standard deviations in parentheses.
t_{max} values are median with range values in parentheses.

Eslicarbazepine:

Following oral administration of ESL 400 mg, 800 mg, and 1200 mg, eslicarbazepine tmax 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 ESL 400 mg, 800 mg, and 1200 mg, respectively.

Systemic exposure to eslicarbazepine appears to be dose-proportional following oral administration of ESL 400 mg, 800 mg and 1200 mg. To assess the "dose-proportionality" of eslicarbazepine plasma concentrations following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD, both Cmax and AUC0-24 ratios in relation with the correspondent ESL dose were calculated. Figures B and C displays the eslicarbazepine Cmax/ESL dose and AUC0-24 /ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD, respectively, as shown in the Figures below:

Figure. Box-plot of eslicarbazepine (BIA 2-194) Cmax/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD

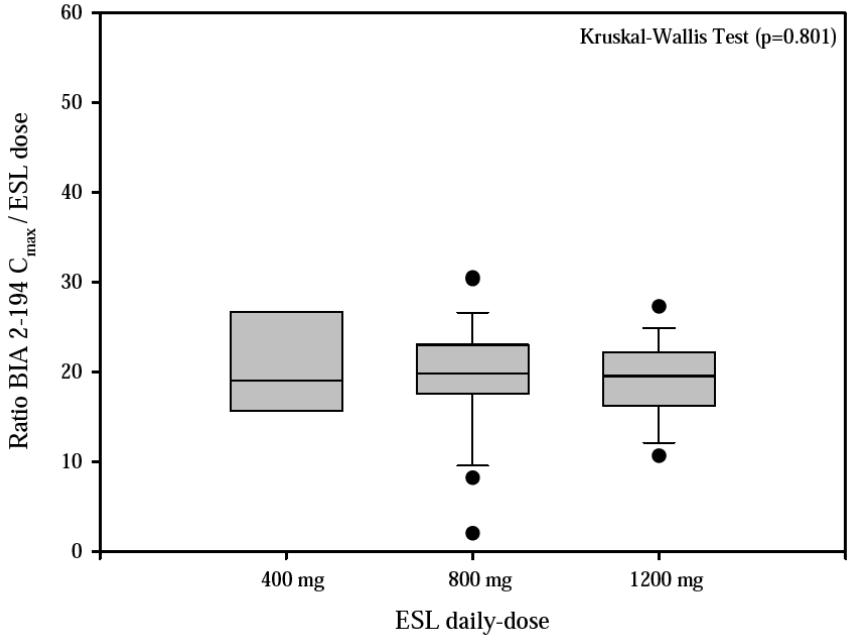
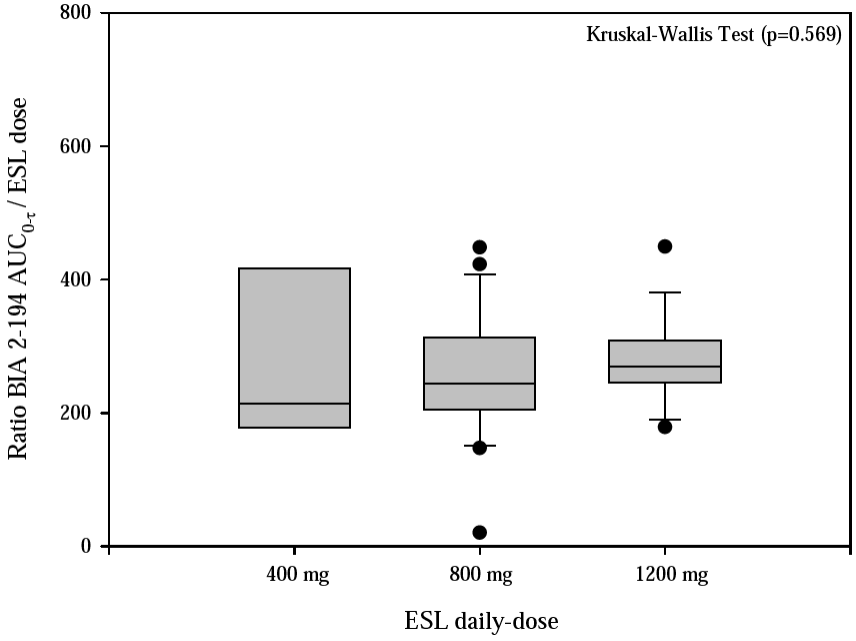


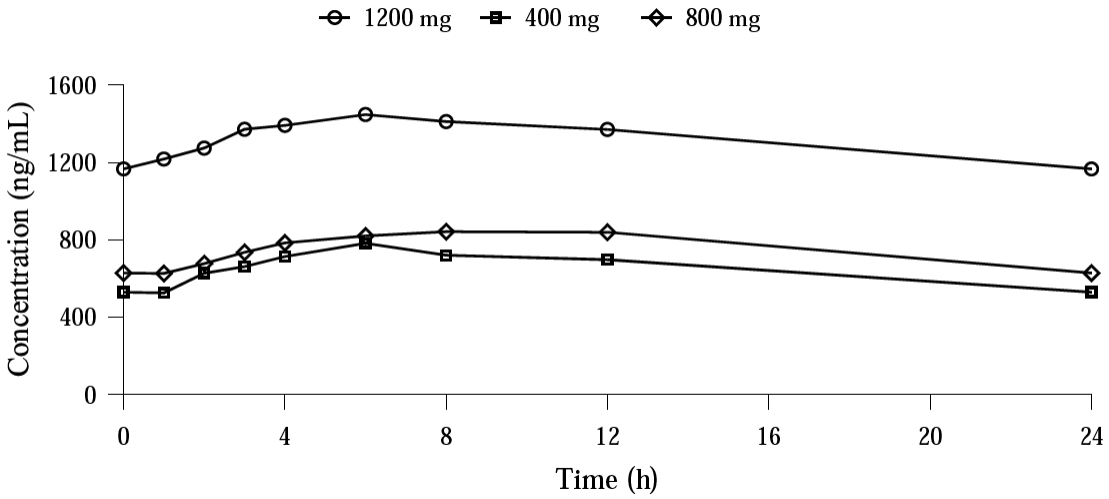
Figure. Box-plot of eslicarbazepine (BIA 2-194) AUC0-24/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



<u>R-licarbazepine:</u>

Mean concentration-time profiles for R-licarbazepine following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD are displayed in the following Figure:

Figure. Mean R-licarbazepine (BIA 2-195) plasma concentration-time profiles following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



Dose proportionality assessment is given below:

Figure. Box-plot of R-licarbazepine (BIA 2-195) Cmax/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD

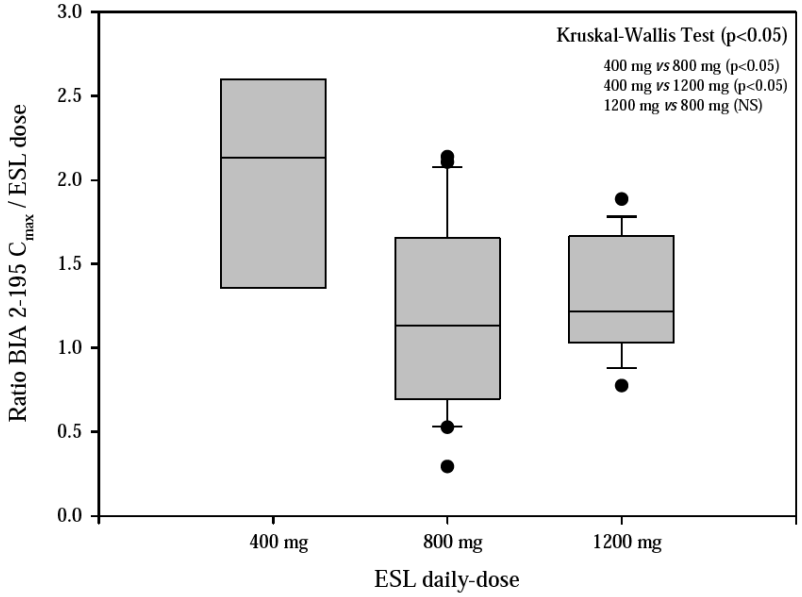
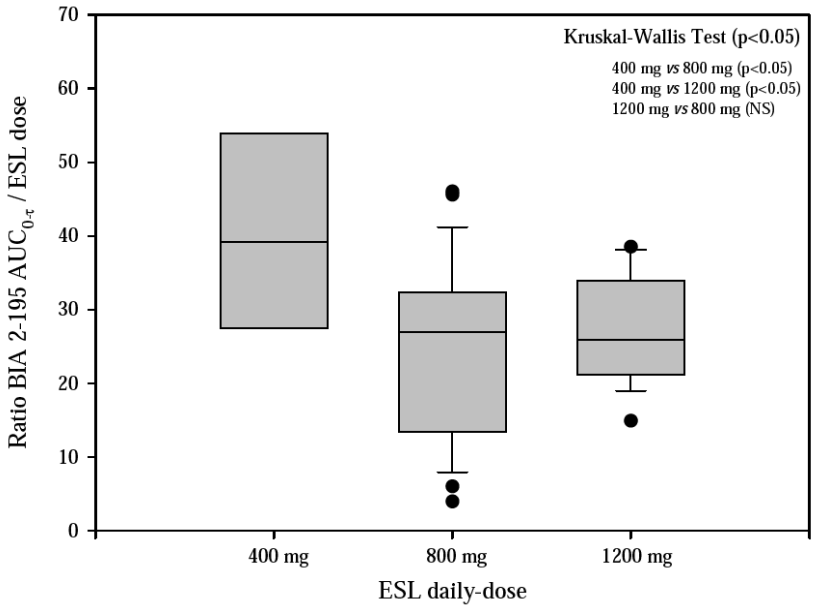


Figure . Box-plot of R-licarbazepine (BIA 2-195) AUC0-24/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



Regarding R-licarbazepine, the kinetic seems to be linear following oral administration of ESL 800 mg, and 1200 mg QD, although differences were found for both parameters (Cmax and AUC0-24) when ESL 400 mg QD were compared with the mentioned higher doses

Oxcarbazepine (OXC)

Mean pharmacokinetic profiles at the three doses and the dose proportionality assessment is given below in the following Figures:

Figure. Mean oxcarbazepine (OXC) plasma concentration-time profiles following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD

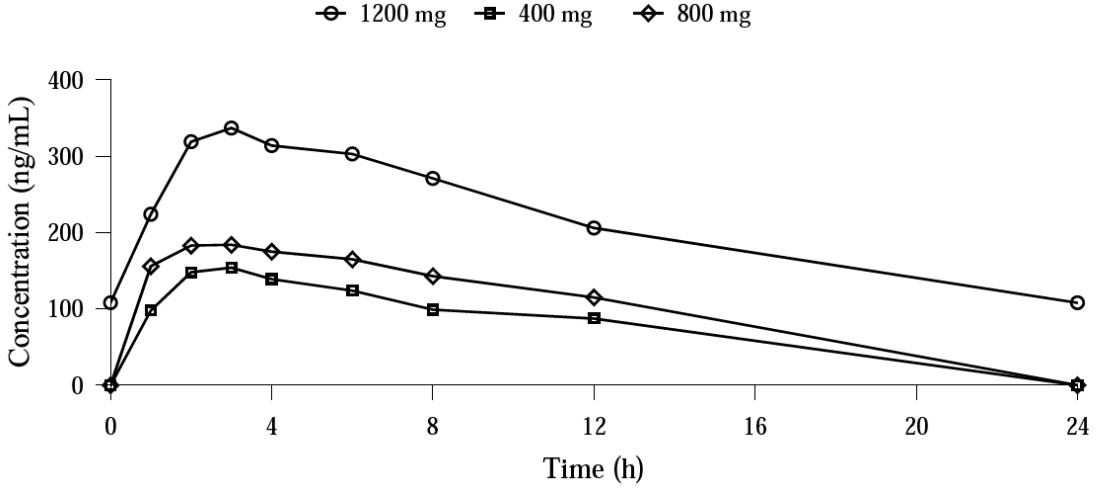


Figure. Box-plot of oxcarbazepine (OXC) Cmax/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD

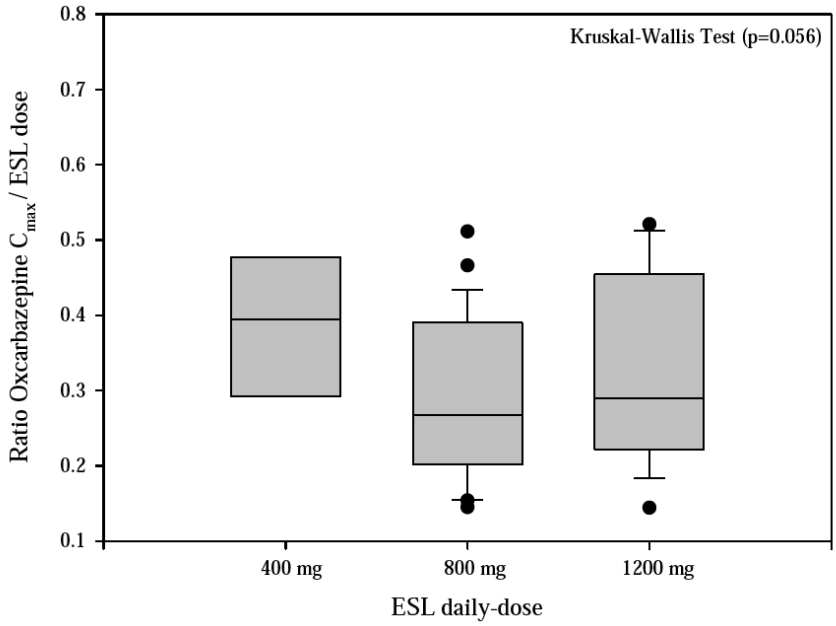
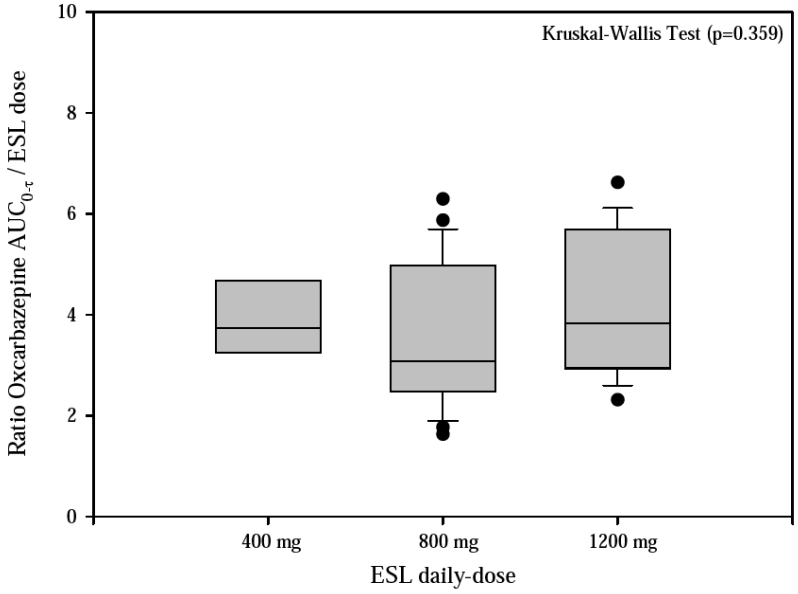


Figure. Box-plot of oxcarbazepine (OXC) AUC0-24/ESL dose ratios following multiple oral doses of ESL 400 mg, 800 mg and 1200 mg QD



Oxcarbazepine AUC0-24 appears to be approximately linear

RELATIVE BIOAVAILBILITY

Study 122: A Single Dose Crossover Comparative Bioavailability Study of Eslicarbazepine Acetate 400 mg, 600 mg and 800 mg Tablets Clinical Trial Formulation (CTF) versus the To-Be-Marketed Formulation (TBM) in Healthy Male and Female Volunteers / Fasting State

Objectives:

To evaluate and compare the relative bioavailability and therefore the bioequivalence of three doses (400 mg, 600 mg and 800 mg) of eslicarbazepine acetate for two formulations (CTF versus TBM) after a single oral dose administration under fasting conditions.

The study design is as follows:

Study Design	Single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design.
Study Population	N=60 Healthy subjects (20 per dose group), 1 dropout Subject #034 was withdrawn after dosing of period 1 for pharmacokinetic reasons (missing the two last blood draws as per SOP PHP-3008) and received only one single oral dose of Eslicarbazepine acetate 600 mg tablets (CTF). Age: 19-54 years (mean 35 years) Gender: 30 males and 30 females Weight: 49.7-97.8 kg (mean 69.4 kg)
Treatment Group	Group 1/ 400 mg: 20 Group 2/ 600 mg: 19 Group 3/ 800 mg: 20 Test-1: One Eslicarbazepine acetate (BIA 2-093) 400 mg tablet (TBM), PD269M-001 Reference-1: One Eslicarbazepine acetate (BIA 2-093) 400 mg tablet (CTF), 050058-L Test-2: One Eslicarbazepine acetate (BIA 2-093) 600 mg tablet (TBM), PD270M-001 Reference-2: One Eslicarbazepine acetate (BIA 2-093) 600 mg tablet (CTF), 050059-L Test-3: One Eslicarbazepine acetate (BIA 2-093) 800 mg tablet (TBM), PD271M-001 Reference-3: One Eslicarbazepine acetate (BIA 2-093) 800 mg tablet (CTF), 060179-L
Dosage and Administration	A single oral dose was administered under fasting conditions in each study period. Each period was separated by a wash-out of 7 days. Diet: A single dose of the assigned formulation was administered orally with 240 mL of water. Meals were provided no less than 4 hours after drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and 2 hours after drug administration. Subjects who were light-smokers were requested to abstain from smoking for 2 hours prior to drug

	administration and until 4 hours after drug administration. Volunteers were instructed to avoid alcohol and food or beverages containing xanthines for 58 hours and food or beverages containing grapefruit for 7 days prior to dosing and during each study period.
Sampling: Blood	For plasma BIA 2-093 and BIA 2-005: Plasma samples were obtained prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 48 and 72 hours after drug administration.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation Plasma BIA 2-093 10 ng/ml BIA 2-005 10 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 10 – 1000 ng/mL for eslicarbazepine acetate and 10 – 10000 ng/mL for BIA 2-005 (S-licarbazepine) + (R-licarbazepine). Quality control concentrations: 30, 1200 and 7500 ng/ml for BIA 2-005; 30, 200 and750 ng/ml for for BIA 2-093 Inter-day precision: % CV: < 4.1 %for BIA 2-005 <4.4% % for BIA 2-093 Inter-day accuracy: 98.1-106.2 % for BIA 2-005, 95.7-101.9% for BIA 2-093 Stability: 22.7 hours at room temp for BIA 2-093 and 7 hours for BIA 2-005, 3 freeze-thaw cycles, at 4C for 83 days
PK Assessment	AUCT, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

The pharmacokinetic parameters for BIA 2-005 for the 400, 600 and 800 mg strengths and the 90% CI for the test/reference are given in the following Tables:

Reviewer's analysis also showed results similar to the sponsor.

Table. Comparison of Results with Standards for Bioequivalence- Group 1 (400 mg)

PARAMETER	TEST-1		REFERENCE-1	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	7107.7	28.2	6660.3	23.2
ln (C_{max})	8.8309	3.2	8.7786	2.6
T_{max} (hours) *	2.00	44.3	2.50	49.7
AUC_T (ng·h/mL)	125739.8	23.1	122134.1	22.6
ln (AUC_T)	11.7158	2.0	11.6878	2.0
AUC_∞ (ng·h/mL)	127071.4	23.5	123419.5	22.9
ln (AUC_∞)	11.7253	2.1	11.6975	2.0
$AUC_{T/\infty}$ (%)	99.06	1.5	99.05	1.5
K_{el} ($hour^{-1}$)	0.0783	20.8	0.0783	18.9
$T½_{el}$ (hours)	9.36	28.9	9.31	28.5

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	10.4	6842.4	6493.5	105.37	99.57	111.52
AUC_T	6.6	122490.8	119115.2	102.83	99.19	106.61
AUC_∞	6.7	123666.5	120267.1	102.83	99.13	106.66

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Table. Comparison of Results with Standards for Bioequivalence- Group 2 (600 mg)

PARAMETER	TEST-2		REFERENCE-2	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	10724.8	18.1	10404.5	16.5
ln (C_{max})	9.2639	2.0	9.2371	1.8
T_{max} (hours) *	2.50	48.5	3.00	43.3
AUC_T (ng·h/mL)	219560.8	18.1	215750.4	20.6
ln (AUC_T)	12.2827	1.6	12.2604	1.8
AUC_∞ (ng·h/mL)	222887.1	18.4	219121.9	20.9
ln (AUC_∞)	12.2971	1.6	12.2752	1.8
$AUC_{T/\infty}$ (%)	98.58	1.3	98.54	1.3
K_{el} ($hour^{-1}$)	0.0701	24.2	0.0701	24.3
$T½_{el}$ (hours)	10.43	23.2	10.47	24.7

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	9.6	10528.4	10256.4	102.65	97.27	108.33
AUC_T	6.0	215972.7	210905.2	102.40	99.00	105.93
AUC_∞	6.0	219172.8	214082.2	102.38	98.97	105.90

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Table. Comparison of Results with Standards for Bioequivalence- Group 3 (800 mg)

PARAMETER	TEST-3		REFERENCE-3	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	13186.4	17.5	12767.6	19.8
ln (C_{max})	9.4724	1.8	9.4317	2.5
T_{max} (hours) *	3.00	54.5	3.00	43.6
AUC_T (ng·h/mL)	294749.1	16.3	293959.9	16.8
ln (AUC_T)	12.5806	1.3	12.5772	1.4
AUC_∞ (ng·h/mL)	299320.3	16.5	299996.9	17.1
ln (AUC_∞)	12.5957	1.4	12.5968	1.4
$AUC_{T/\infty}$ (%)	98.51	0.8	98.08	2.2
K_{el} ($hour^{-1}$)	0.0649	21.4	0.0648	19.8
$T_{½el}$ (hours)	11.05	17.2	11.10	19.9

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	16.0	12996.6	12477.9	104.16	95.44	113.67
AUC_T	4.6	290868.7	289882.3	100.34	97.85	102.90
AUC_∞	4.1	295275.3	295621.9	99.88	97.65	102.16

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Conclusions:

The To-Be-Marketed formulations (Eslicarbazepine acetate 400 mg tablets, 600 mg tablets and 800 mg tablets manufactured by (b) (4) are judged to be bioequivalent to the respective Clinical Trial formulations (Eslicarbazepine acetate 400 mg tablets, 600 mg tablets and 800 mg tablets manufactured by BIAL-Portela & Ca, S.A., Portugal) under fasting conditions.

Study 109: A Single Dose Crossover Comparative Bioavailability Study of an oral suspension and two tablet formulations of BIA 2-093 in healthy volunteers

Objectives:

To investigate the bioavailability and bioequivalence of three different formulations of BIA 2-093: oral suspension 50 mg/mL, tablet strength 200 mg and tablet strength 800 mg.

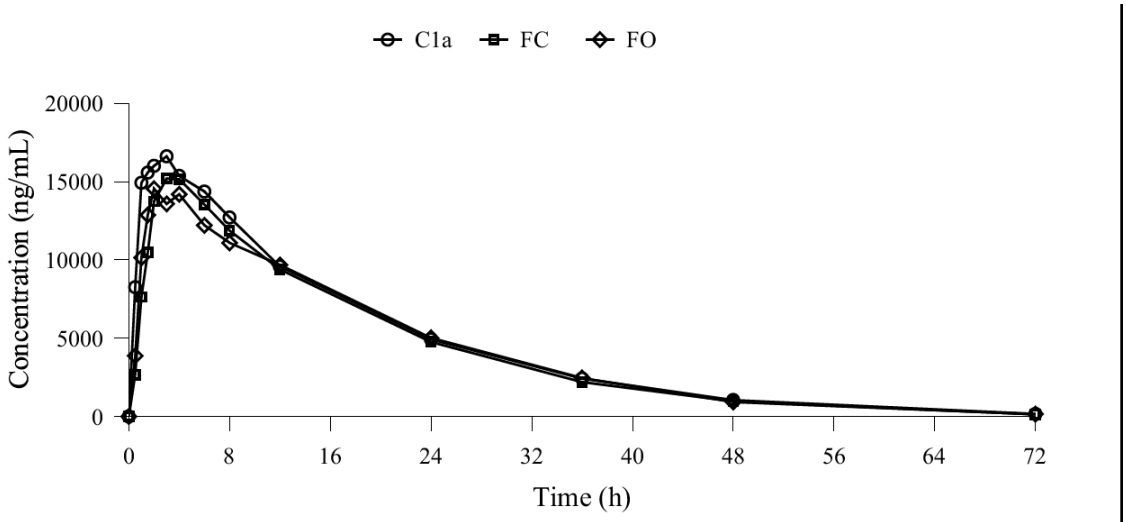
The study design is as follows:

Study Design	Single centre, open-label, randomized, three-way crossover study in 18 healthy subjects The study consisted of three consecutive single-dose treatment periods separated by a washout period of 7 days or more. On each treatment period, the volunteers received a single dose of BIA 2-093 800 mg, orally, either in the form of *Test 1*, *Test 2* or *Reference* formulation.
Study Population	N=18 Healthy subjects Age: 19-32 years (mean 22.72 years) Gender: 9 males and 9 females Weight: 47.5-74.5 kg (mean 65.1 kg)
Treatment Group	Test-1: 16 mL of 50 mg/mL BIA 2- 093 oral suspension Test-2: four 200 mg BIA 2-093 tablets Reference-1: one 800 mg BIA 2-093 tablet
Dosage and Administration	A single oral dose was administered under fasting conditions in each study period. Each period was separated by a wash-out of 7 days. Diet: A single dose of the assigned formulation was administered orally with 240 mL of water. Meals were provided no less than 4 hours after drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and 2 hours after drug administration. Subjects who were light-smokers were requested to abstain from smoking for 2 hours prior to drug administration and until 4 hours after drug administration. Volunteers were instructed to avoid alcohol and food or beverages containing xanthines for 58 hours and food or beverages containing grapefruit for 7 days prior to dosing and during each study period. Batch number BIA 2-093 oral suspension 50 mg/mL (formulation C1a) 040014-L BIA 2-093 tablets 200 mg (formulation FO) 040012-L BIA 2-093 tablets 800 mg (formulation FC) 040013-L
Sampling: Blood	For plasma BIA 2-093 and BIA 2-005: Plasma samples were obtained prior to and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 48 and 72 hours after drug administration.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation

	Plasma BIA 2-093 10 ng/ml BIA 2-005 10 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 10 – 1000 ng/mL for eslicarbazepine acetate and 10 – 10000 ng/mL for BIA 2-005 (S-licarbazepine) + (R-licarbazepine). Quality control concentrations: 10, 25, 400, 700, 1000 for BIA 2-093 and 1600 and 10000 ng/ml also for BIA 2-005. Dilutions done as well. Inter-day precision: % CV: < 5.52 %for BIA 2-005 <5.79% % for BIA 2-093 Inter-day accuracy: 98-105 % for BIA 2-005, 94-101% for BIA 2-093 Stability: 22.7 hours at room temp for BIA 2-093 and 7 hours for BIA 2-005, 3 freeze-thaw cycles, at 4C for 83 days
PK Assessment	AUCT, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

Mean concentration-time profiles for BIA 2-005 are given below:



C1a = *Test 1* (oral suspension 50 mg/mL); FO = *Test 2* (tablets 200 mg); *FC* = Reference (tablet 800 mg)

The corresponding main pharmacokinetic parameters were as follows:

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
Test 1 (C1a)	18048 (4644)	2 (1-4)	323277 (64055)	325732 (64898)	0.0740 (0.0138)	9.69 (1.83)
Test 2 (FO)	16007 (4008)	3 (1.5-6)	302026 (65270)	304219 (66045)	0.0767 (0.0135)	9.33 (1.79)
Reference (FC)	17042 (4131)	3 (1-4)	299016 (58806)	301065 (59957)	0.0761 (0.0136)	9.40 (1.76)

Results expressed as arithmetic means with the corresponding standard deviations (sd) in parentheses.
t_{max} values are median with range values in parentheses.

The point estimates (PE) and 90% CI for the comparison of BIA 2-005 pharmacokinetic parameters between *Test* formulations and *Reference* formulation can be summarized as follows:

BIA 2-005		*Test 1 / Reference*	*Test 2 / Reference*
C_{max}	PE	1.067	0.941
	90% CI	0.970;1.153	0.861;1.023
$AUC_{0-\infty}$	PE	1.092	0.993
	90% CI	1.012;1.154	0.942;1.074

A statistically significant (p=0.016) decrease in tmax was observed when *Test 1* and *Reference* formulations were compared. No difference was found between tmax when *Test 2* was compared with *Reference* formulations.

Overall Conclusions:

No significant differences were found for the BIA 2-005 Cmax and AUC0-∞ parameters following a single oral dose of 800 mg BIA 2-093 between *Test* (C1a and FO) and *Reference* (FC) formulations. Thus, the *Test* formulations (C1a and FO) exhibited a very similar pharmacokinetic profile in comparison with *Reference* formulation (FC) and they can be considered as bioequivalent.

FOOD EFFECT

Study 103: Tolerability and Effect of food on the pharmacokinetics of a single 800 mg oral dose of BIA 2-093 in Healthy Male Volunteers

Objectives:

To investigate the effect of food on the pharmacokinetics of BIA 2-093 and its metabolites following the administration of a single oral dose of 800 mg of BIA 2-093 to healthy volunteers.

The study design is as follows:

Study Design	Open-label, balanced randomized, 2-way crossover study of single oral 800 mg doses of BIA 2-093. The two treatment periods of the study were separated by a washout period of 14 days or more.
Study Population	N=12 Healthy subjects Age: 20-45 years (mean 26.16 years) Gender: 6 males and 6 females Weight: 60-93-97.8 kg (mean 73.68 kg)
Treatment Group	4x200 mg: fasted 4x200 mg: fed BIA 2-093 tablets, 200 mg, Batch 10063 (4 tablets used) . This is not the highest strength and also not the to-be marketed formulation.
Dosage and Administration	Subjects received single doses of BIA 2-093 on two different occasions, administered in the form of oral tablets, given with 200 mL potable water. The dose level investigated was 800 mg. Diet: Subjects were requested to fast overnight for at least 10 hours before each morning dose. According to the randomization schedule, on the appropriate occasions the subject remained fasted until approximately 4 hours after dosing or the fasting was broken by a standard high-fat content breakfast prior to dosing. A standard lunch was provided at approximately 4 hours post-dose, a snack 8 hours postdose and a dinner 12 hours post-dose. Water *ad libitum* was allowed. The standard high-fat content breakfast was composed of 2 eggs scrambled in butter, 2 strips of bacon, 2 slices of buttered toasted white bread and corn flakes with 200 mL of whole milk. The breakfast was eaten within 30 minutes and drug administration occurred immediately, thereafter.
Sampling: Blood	For plasma BIA 2-093 and BIA 2-005 and oxcarbazepine: Plasma samples were obtained prior to and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours post-dose.
Urine	none
Feces	none
Analysis	HPLC/MS method

	Lower Limits of Quantitation Plasma BIA 2-093 10 ng/ml BIA 2-005 10 ng/ml Oxcarbazepine 10 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 10 – 1000 ng/mL for eslicarbazepine acetate and 10 – 1000 ng/mL for BIA 2-005 (S-licarbazepine) + (R-licarbazepine) and oxcarbazepine. Quality control concentrations: 30, 1200 and 7500 ng/ml for BIA 2-005; 30, 200 and750 ng/ml for for BIA 2-093 Inter-day precision: % CV: < 6.0 %for BIA 2-005 <6.4% % for BIA 2-093 4.6 % for oxcarbazepine Inter-day accuracy: 96.5-105.6 % for BIA 2-005, 97.4-102% for BIA 2-093 98.7-101.7 % for oxcarbazepine
PK Assessment	AUCT, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

Plasma levels were below the limit of quantification (10 ng/mL) in almost all the sampling times for BIA 2-093.

The mean pharmacokinetic parameters of BIA 2-005 and Oxcarbazepine under fed and fasted conditions are given in the following Tables:

Table: Pharmacokinetic parameters of BIA 2-005 following oral administration of 800 mg of BIA 2-093 in fasting and in fed conditions (n=12)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
Fasting	11302 (1866)	3.5 (0.5-8.0)	243155 (31213)	243589 (31052)	0.0780 (0.00814)	8.98 (0.992)
Fed	12799 (1768)	4.0 (0.5-8.0)	229350 (41366)	242459 (32085)	0.0721 (0.0107)	9.83 (1.62)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
t_{max} values are median with range values in parentheses.

Table: Pharmacokinetic parameters of Oxcarbazepine following oral administration of 800 mg of BIA 2-093 in fasting and fed conditions (n=12)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	λ_z (1/h)	$t_{1/2}$ (h)
Fasting	110 (20.6)	4.0 (2.0-12.0)	2327 (431)	2646 (330)	0.0547 (0.00953)	13.0 (2.02)
Fed	128 (43.3)	3.0 (1.0-6.0)	2239 (619)	2576 (599)	0.0568 (0.00447)	12.3 (0.910)

The Table below presents the point estimates and 90% CI for the comparison of Cmax and AUC0-∞ for BIA 2-005.

Table: Point estimates (PE) and 90% confidence intervals (90% CI) for the comparison of Cmax and AUC0-∞ of BIA 2-005 following oral administration of 800 mg of BIA 2-093 in fasting and fed conditions

		BIA 2-005 Fed/Fasting
C_{max} (ng/mL)	PE	1.14
	90% CI	1.04; 1.25
$AUC_{0-\infty}$ (ng.h/mL)	PE	1.00
	90% CI	0.95; 1.04

- High Fat meal did not affect the AUC and Cmax of BIA 2-005. The 90% CI was within the acceptable limits of bioequivalence.
- No statistical differences were found between t_{max} values for BIA 2-005 following administration of BIA 2-093 in fasting and fed conditions.

The Table below presents the point estimates and 90% CI for the comparison of Cmax and AUC0-∞ for Oxcarbazepine.

Table: Point estimates (PE) and 90% confidence intervals (90% CI) for the comparison of C_{max} and $AUC_{0-\infty}$ of Oxcarbazepine following oral administration of 800 mg of BIA 2-093 in fasting and fed conditions

		Oxcarbazepine Fed/Fasting
C_{max} (ng/mL)	PE	1.13
	90% CI	1.04; 1.22
$AUC_{0-\infty}$ (ng.h/mL)	PE	0.96
	90% CI	0.89; 1.04

- High Fat meal did not affect the AUC and Cmax of oxcarbazepine. The 90% CI was within the acceptable limits of bioequivalence.
- No statistical differences were found between t_{max} values for oxcarbazepine following administration of BIA 2-093 in fasting and fed conditions.

Overall Conclusions:

- Neither the BIA 2-005 nor the Oxcarbazepine kinetic profiles were influenced by the presence of food.

Reviewer's Comment: The food effect study was not done on the highest strength, 800 mg. Instead it was done on a 200 mg strength. The sponsor has conducted another study with highest strength of the to-be-marketed formulation. Hence, this can be only considered supportive.

FOOD EFFECT AND DOSAGE FORM PROPORTIONALITY
(TBM formulation)
Study 117: Food effect and dosage form proportionality study of eslicarbazepine acetate market formulation in healthy volunteers

Objectives:

Study A: To investigate the effect of food on the pharmacokinetics of eslicarbazepine acetate following administration of an 800 mg tablet from the to-be-marketed formulation of eslicarbazepine acetate in healthy volunteers.
Study B: To investigate the dosage form proportionality between the 400 mg and 800 mg tablet strengths of the to-be-marketed formulation of eslicarbazepine acetate in healthy volunteers.

The study design is as follows:

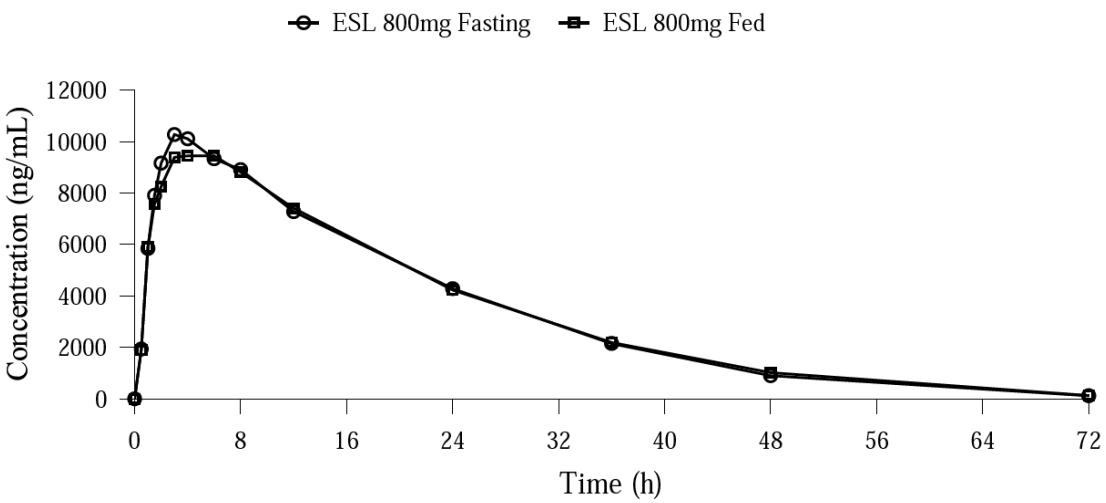
Study Design	Single-centre, open-label, randomized, gender-balanced, 3-way crossover, 3-period, 3-sequence study in 18 healthy male and female subjects. The study consisted of 3 periods separated by a washout of 7 days or more between doses. Subjects received a single oral 800 mg dose of eslicarbazepine acetate following a standard meal in one period, and following at least 10 hours of fasting in two periods.
Study Population	N=18 Healthy subjects enrolled, 17 completed Age: 21-30years (mean 24.39 years) Gender: 9 males and 9 females Weight: 47-87 kg (mean 65.89 kg)
Treatment Group	A: 800 mg single-dose following a standard meal and B: 800 mg single dose following at least 10 hours of fasting C: 800 mg dose administered in the form of 2 x 400 mg tablets Washout=7 days
Dosage and Administration	oral tablets were given with 240 mL potable water. The batch numbers of ESL formulations used in this study were as follows: Batch number ESL 400 mg tablets PD269M-001 ESL 800 mg tablets PD271M-001 Diet: Subjects were requested to fast overnight for at least 10 hours before each morning dose. According to the randomization schedule, on the appropriate occasions the subject remained fasted until approximately 4 hours after dosing or the fasting was broken by a standard high-fat content breakfast prior to dosing. A standard lunch was provided at approximately 4 hours post-dose, a snack 8 hours postdose and a dinner 12 hours post-dose. Water *ad libitum* was allowed.

	The standard high-fat content breakfast was composed of 2 eggs scrambled in butter, 2 strips of bacon, 2 slices of buttered toasted white bread and corn flakes with 200 mL of whole milk. The breakfast was eaten within 30 minutes and drug administration occurred immediately, thereafter.
Sampling: Blood	<u>For plasma BIA 2-093 and BIA 2-005 and oxcarbazepine:</u> Plasma samples were obtained prior to and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours post-dose.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation <u>Plasma</u> BIA 2-093 10 ng/ml BIA 2-005 10 ng/ml <u>Plasma:</u> Method: LC/MS/MS method Linear Range: 10 – 25000 ng/mL for eslicarbazepine acetate and 10 – 25000 ng/mL for BIA 2-005 (S-licarbazepine) + (R-licarbazepine). Quality control concentrations: 30, 1000 and 20000 ng/ml for BIA-2005 and BIA 2-093 Inter-day precision: % CV: < 5.4 %for BIA 2-005 <5.1% % for BIA 2-093 Inter-day accuracy: 91.5-106 % for BIA 2-005, 91-109% for BIA 2-093
PK Assessment	AUCT, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

<u>Pharmacokinetic Results:</u>

<u>Food Effect:</u>
Mean BIA 2-005 plasma concentration-time profiles following a single oral dose of ESL 800 mg in fasting (*Reference*) and fed (*Test1*) conditions are displayed in Figure A below.

Figure A. Mean BIA 2-005 plasma concentration-time profiles following a single oral dose of ESL 800 mg in fasting (*Reference*) and fed (*Test1*) conditions (n=17)



The pharmacokinetic parameters are given below:

Table: Arithmetic Mean (SD) Pharmacokinetic Parameters of (RS)-licarbazepine Following a Single SEP-0002093 800 mg Dose in Fasting (Reference) and Following a Standard Meal (Test)

	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\tau}$ (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
Reference (fasting)	11,288 (2,628)	3 (1-6)	246,504 (50381)	248,638 (50,464)	10.2 (1.36)
Test (standard meal)	11,299 (2,495)	3 (1-8)	239,066 (50,510)	241,074 (50,764)	10.2 (1.13)

t_{max} are median values with range in parentheses

The point estimates and the 90% confidence intervals demonstrating the effect of food is given below:

BIA 2-005 pharmacokinetic parameters		***Test1/Reference***
C_{max}	PE (%)	100.96
	90% CI	94.08; 108.35
AUC_{0-t}	PE (%)	96.79
	90% CI	94.34; 99.32
$AUC_{0-\infty}$	PE (%)	96.75
	90% CI	94.27; 99.29

PE – Point estimate; 90% CI – 90% confidence intervals

Bioequivalence criteria between *Test* and *Reference* were met because the 90% confidence interval for all parameters under consideration (AUC0-∞, AUC0-t, and Cmax) is contained within the 80 - 125% interval.
In conclusion, the presence of food did not change the pharmacokinetics of SEP-0002093 following oral administration of an 800 mg tablet from the to-be-marketed formulation.

Dosage Form Proportionality:

Mean BIA 2-005 concentration-time profiles following a single oral dose of ESL 800 mg in the form of 1x800 mg tablet (*Reference*) and in the form of 2x400 mg tablets (*Test2*), both in fasting conditions were superimposible.

The pharmacokinetic parameters of the two treatments is given below:

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
ESL 800 mg (1 x 800 mg) in fasting (*Reference*)	11288 (2628)	3.00 (1.0-6.0)	246504 (50381)	248638 (50464)	10.1 (1.4)
ESL 800 mg (2x400 mg) in fasting (*Test2*)	11353 (2748)	2.00 (1.0-6.0)	246973 (48599)	249429 (48873)	10.1 (1.5)

Results expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses
t_{max} values are median with range values in parentheses

The point estimates and the 90% confidence intervals demonstrating the effect of food is given below:

BIA 2-005 pharmacokinetic parameters		***Test2/Reference***
C_{max}	PE (%)	100.78
	90% CI	93.91; 108.16
AUC_{0-t}	PE (%)	100.37
	90% CI	97.82; 102.99
$AUC_{0-\infty}$	PE (%)	100.48
	90% CI	97.91; 103.13

PE – Point estimate; 90% CI – 90% confidence intervals

Dosage strength proportionality was established between 2x400 mg and 1x800 mg.

Overall conclusions:

- The presence of food had no significant effect on the pharmacokinetics of ESL and, therefore, ESL can be administered without regard to meals without any significant effect on BIA 2-005 drug disposition and extent of systemic exposure.
- BIA 2-005 bioavailability was similar when an ESL 800 mg oral single-dose was

administered in the form of 1 x 800 mg tablet or in the form of 2 x 400 mg tablets. (b) (4)

INTRINSIC FACTORS

Study 105: Single-dose and steady-state pharmacokinetics of BIA 2-093 and its metabolites in healthy elderly subjects compared with those in healthy young subjects.

Objectives:

- To determine the effects of age on the pharmacokinetic profile of BIA 2-093 and its active metabolites.
- To evaluate the clinical tolerability and safety of BIA 2-093 administered to healthy young and elderly volunteers.

The study design is as follows:

Study Design	This was a single-centre, open-label, parallel group, non-randomized study with a single dose phase (Phase A) followed by a multiple-dose phase (Phase B), in 12 healthy elderly and 12 healthy young subjects.
Study Population	N=16 Healthy Young subjects, 14 Elderly Age: 18-38 years (mean 29.9 years) 65-80 years (mean 69.6 years) Gender: 8 males and 8 females: Young 7 males and 7 females: Elderly Weight: 48-98 kg (mean 70.7 kg) 55-103 Kg (mean 77.3 kg) Race: All White
Treatment Group	Young Elderly The study was to be performed in two phases: Phase A (single-dose) and B (multiple-dose, once daily for 7 Days). BIA 2-093: 600 mg
Dosage and Administration	During the whole study, subjects were to receive a single 600 mg dose of BIA 2-093 (Phase A) followed by 600 mg BIA 2-093 once daily for 8 days in Phase B. Phase B was to begin 96 hours post-Phase A dose. In Phase A subjects received a single dose of 600 mg BIA 2-093 in Day 1, after a fasting of at least 8 hours, orally, with 200 ml of potable water. The dosing was to occur between 08:00 and 09:00 am. In Phase B subjects received a 600 mg dose of BIA 2-093 from Day 5 to Day 12, orally, with 200 ml of potable water. The dosing was to occur between 08:00 and 09:00, without regard of meals on Days 5-11 and after a fasting period of at least 8 hours on Day 12. Batch number 600mg (Batch 20168)
Sampling: Blood	For BIA 2-093 and metabolites: *Single-dose period*: Day 1 at pre-dose, and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours post-dose. *Multiple-dose period:* from Day 5 to Day 11 inclusive, early in the morning, before the daily dose (for trough levels). Day 12: pre-dose,

	and ½, 1, 1½, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours post-last dose.
Urine	For BIA 2-093 and metabolites: *Single-dose period*: Day 1: Pre-dose, 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, and 72-96 hours post-dose. *Multiple-dose period*: Day 12: Predose, 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, and 96-120 hours post-last dose.
Feces	none
Analysis	Lower Limits of Quantitation Plasma BIA 2-093 50 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml Oxcarbazepine 50 ng/ml Plasma: Method: HPLC/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 10000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 200, 4000, 8000 ng/ml for BIA 2-194 and BIA 2-195; 100, 400 and 800 and 2000 ng/ml for oxcarbazepine Inter-day precision: % CV: < 9.6 %for BIA 2-194 and BIA 2-195 <6.8 % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 96-99% for BIA 2-194 and BIA 2-195, 91-92% for BIA 2-093 and oxcarbazepine.
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, R0
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

Effect of Age:

The pharmacokinetic parameters for BIA 2-194, BIA 2-195 and oxcarbazepine in young and elderly is shown the following Tables:

Table: Mean pharmacokinetic parameters of BIA 2-093 metabolites in the Young subjects:

	BIA 2-194		BIA 2-195		Oxcarbazepine	
	Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose
C_{max} (ng/mL)	9867 (1714)	17309 (3430)	192 (31.5)	461 (132)	77.3* (15.6)	150 (36.6)
t_{max} (h)	2.5 (1-6)	1.5 (1-6)	10 (4-24)	8 (3-12)	6* (1-12)	2.5 (1-6)
$AUC_{0-\tau}$ (ng.h/mL)	137354 (24742)	213815 (41889)	2980 847	8542 (2388)	914** 323	1804 (0327)
$AUC_{0-\infty}$ (ng.h/mL)	180899 (37624)	296702 (67577)	NA	18363** (4095)	NA	2820*** (821)
$t_{1/2}$ (h)	10.1 (0.992)	10.5 (1.42)	NA	22.0** (5.50)	NA	14.2*** (4.78)
R_0	-	1.64	-	NA	-	NA

Table: Mean pharmacokinetic parameters of BIA 2-093 metabolites in the Elderly subjects:

	BIA 2-194		BIA 2-195		Oxcarbazepine	
	Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose
C_{max} (ng/mL)	9469 (2284)	15067 (2126)	209* (72.1)	531 (190)	76.3* (29.5)	135 (36.6)
t_{max} (h)	3 (1-6)	2 (1-4)	12* (6-24)	8 (2-12)	6* (2-12)	2 (1-6)
$AUC_{0-\tau}$ (ng.h/mL)	141245 (38438)	208432 (28561)	3867* (1644)	10590 (3158)	784* (689)	1753 (537)
$AUC_{0-\infty}$ (ng.h/mL)	196030 (69152)	294290 (40356)	NA	21787** (6247)	NA	3191*** (397)
$t_{1/2}$ (h)	10.9 (0.916)	11.1 (1.60)	NA	22.1** (7.65)	NA	15.4*** (3.51)
R_0	-	1.59	-	NA	-	NA

Results expressed as arithmetic means with the correspondent standard deviations in parentheses.

For comparison purposes, only BIA 2-194 was analyzed because it represents more than 90% of the systemic drug exposure. Mean concentration versus time profiles of BIA 2-194 in the young and the elderly groups following an oral 600 mg single-dose of BIA 2-093 and following the last dose of an oral 600 mg once-daily regimen of BIA 2-093 for 8 days are illustrated in the following Figures.

Figure. Mean plasma BIA 2-194 concentration-time profiles following an oral 600 mg single-dose of BIA 2-093 in the young and elderly groups

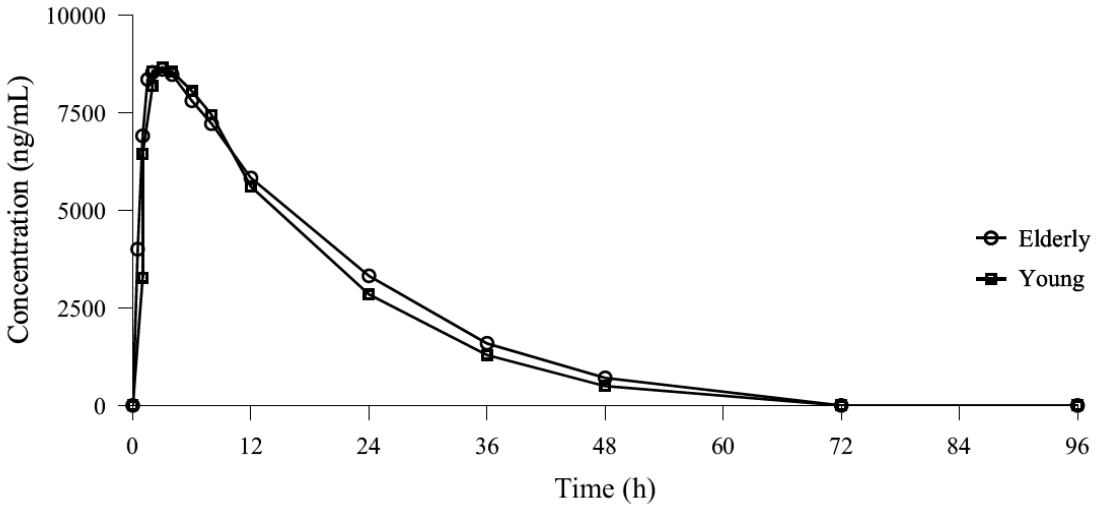
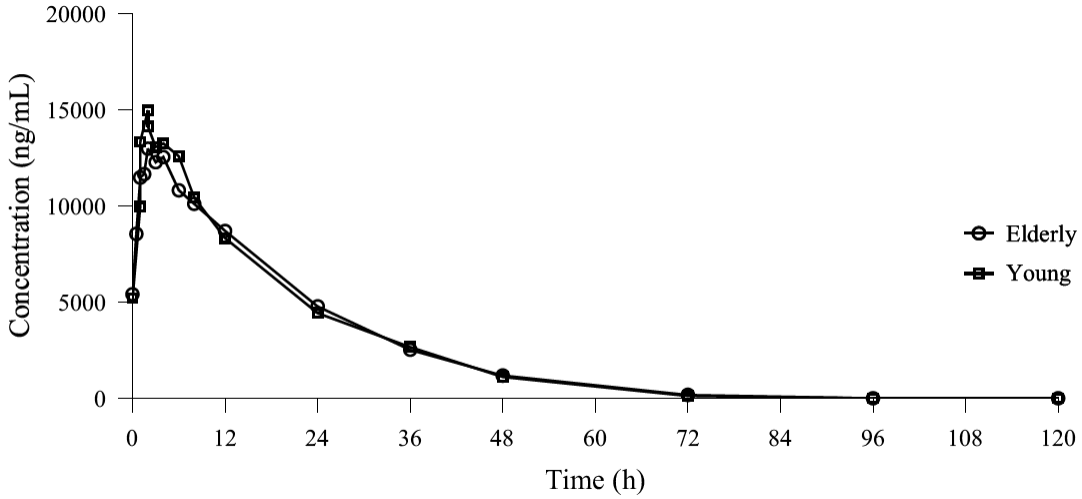


Figure. Mean plasma BIA 2-194 concentration-time profiles following the last dose of a 600 mg once-daily regimen of BIA 2-093 for 8 days in the young and elderly groups



The rate and extent of systemic exposure were compared through the geometric mean ratios of C_{max}, AUC_{τ} (0-24 h) and $AUC_{0-\infty}$ for the main metabolite, BIA 2-194 and are displayed in the following Table:

Table . PK Parameters geometric mean ratios of BIA 2-194 between the elderly and young groups

		Elderly subjects	Young subjects	Ratio (Elderly/Young)	95%CI	*p-value*
C_{max}	Single-dose	9332	9743	0.948	0.812;1.14	0.504 (NS)
	Multiple-dose	14942	16990	0.879	0.771;1.03	0.0781 (NS)
t_{max}	Single-dose	3.00	2.50	-0.0417*	-1.68;1.60	0.930 (NS)
	Multiple-dose	2.00	1.50	0.000*	-1.07;1.07	0.434 (NS)
$AUC_{0-\tau}$	Single-dose	137313	135253	1.02	0.857;1.24	0.699 (NS)
	Multiple-dose	206628	209997	0.980	0.898;1.09	0.813 (NS)
$AUC_{0-\infty}$	Single-dose	187793	177298	1.06	0.879;1.32	0.586 (NS)
	Multiple-dose	291723	289233	1.01	0.887;1.18	0.914 (NS)

C_{max}, $AUC_{0-\tau}$ and $AUC_{0-\infty}$ expressed as geometric mean (ng/mL); t_{max} expressed as median (h).
*Difference (Elderly-Young).
95%CI = 95% Confidence Interval.
NS = Not significant.

Independently of the statistical tools applied (ANOVA, ratios, differences and corresponding 95% confidence intervals), no significant differences were found between elderly and young groups concerning all pharmacokinetic parameters analyzed.

With multiple-dosing, steady-state plasma BIA 2-194 concentrations in young/elderly subjects were attained at 4 to 5 days of once-daily 600 mg BIA 2-093 administration. An estimated accumulation factor (R_0) of 1.64 was determined for BIA 2-194 in the young and 1.59 in the elderly. The Percent of the minor metabolites were similar in the two groups.

Reviewer's Comment: It is important to note that in this study, the elderly group had CrCL ≥ 67 mL/min. Age related reductions in CrCL is possible, in which case higher exposure of eslicarnazepine will be observed.

Effect of Gender:
In young
Mean concentration versus time profiles of BIA 2-194 in young males and females after single and multiple dose administration is shown in the following Figures.

Figure. Mean plasma BIA 2-194 concentration-time profiles following an oral 600 mg single-dose of BIA 2-093 in female and male groups

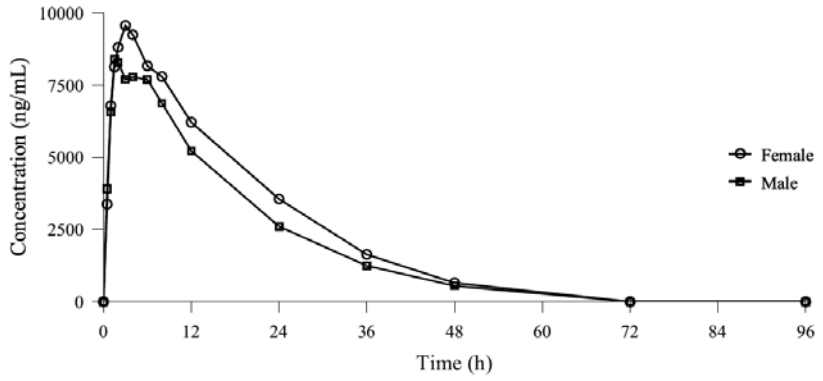
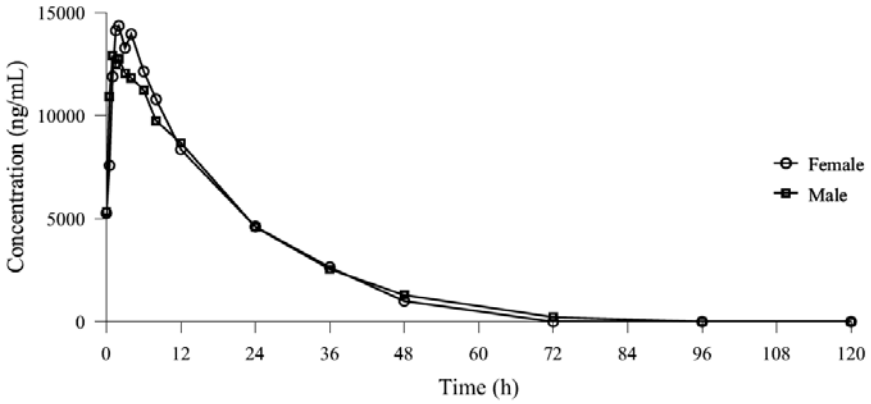


Figure. Mean plasma BIA 2-194 concentration-time profiles following the last dose of a 600 mg once-daily regimen of BIA 2-093 in female and male groups



The PK parameters after single 600 mg in young males and females for the BIA 2-093 is shown in the following Table:

Table. Gender Effect on PK Parameters of BIA 2-093 metabolites in Young after single dose

Metabolite	Female			Male		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
BIA 2-194	9959 (2120)	188678 (37002)	9.92 (1.15)	9775 (1396)	173121 (39999)	10.3 (0.861)
BIA 2-195	189 (35.6)	NA	NA	195 (30.0)	NA	NA
Oxcarbazepine	74.2 (17.6)	NA	NA	81.1* (13.8)	NA	NA

After single dose, female mean BIA 2-194 Cmax and AUC were 2% and 9% higher than male in the young subjects.

Table. Gender Effect on PK Parameters of BIA 2-093 metabolites in Young after multiple doses

Metabolite	Female			Male		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
BIA 2-194	17433 (1654)	302782 (47604)	10.0 (1.33)	17184 (4807)	290623 (87703)	10.9 (1.48)
BIA 2-195	472 (167)	18998** (4992)	19.9** (4.75)	451 (102)	18363 (4095)	22.0 (5.50)
Oxcarbazepine	147 (40.3)	3298** (596)	16.8** (4.14)	152 (36.2)	2436* (818)	12.2* (4.60)

After multiple doses, females mean BIA- 2-194 Cmax and AUC were 1.5 and 4% than males in the young subjects.

In Elderly

Table. Gender Effect on PK Parameters of BIA 2-093 metabolites in Elderly after single dose

	Female			Male		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
BIA 2-194	10210 (2580)	221307 (89542)	10.6 (0.606)	8729 (1871)	170752 (31128)	11.1 (1.15)
BIA 2-195	247 (76.3)	NA	NA	164* (32.9)	NA	NA
BIA 2-194//195	10255 (2544)	229718 (94130)	10.6 (0.557)	8766 (1876)	174694 (33189)	11.1 (1.24)
Oxcarbazepine	86.1 (37.8)	NA	NA	64.6* (8.77)	NA	NA

After single dose, female mean BIA 2-194 Cmax and AUC were 17 and 30% higher than male in the elderly subjects.

Table. Gender Effect on PK Parameters of BIA 2-093 metabolites in Elderly after multiple doses

Metabolite	Female			Male		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
BIA 2-194	16249 (2367)	287651 (44044)	10.7 (0.344)	13886 (993)	300929 (39207)	11.5 (2.26)
BIA 2-195	642 (210)	24552* (3987)	18.2* (4.28)	421 (76.2)	19943 (7106)	24.7 (8.62)
Oxcarbazepine	156 (36.3)	3282** (596)	13.4** (0.989)	114 (23.8)	3122* (251)	16.9* (4.13)

After multiple doses, female mean BIA 2-194 Cmax was 17% higher but AUC 4% lower in the elderly female subjects compared to males.

The rate and extent of systemic exposure were compared between gender groups (young and elderly combined) through the geometric mean ratios of Cmax, AUCτ(0-24 h) and AUC0-∞ for the main metabolite, BIA 2-194 and the results are displayed in the following Tables

Table. PK Parameters geometric mean ratios of BIA 2-194 between the female and male groups

		Female	Male	Ratio (Female/Male)	95%CI	*p-value*
C_{max}	Single-dose	9879	9104	1.09	0.871;1.43	0.331 (NS)
	Multiple-dose	16727	15177	1.10	0.979;1.27	0.219 (NS)
t_{max}	Single-dose	3.00	2.00	0.625*	-0.744;1.99	0.153 (NS)
	Multiple-dose	2.00	1.30	0.667*	-0.453;1.79	0.0852 (NS)
$AUC_{0-\tau}$	Single-dose	146545	126732	1.16	0.948;1.48.	0.0922 (NS)
	Multiple-dose	249920	204148	1.04	0.881;1.28	0.546 (NS)
$AUC_{0-\infty}$	Single-dose	197212	168830	1.17	0.902;1.63	0.127 (NS)
	Multiple-dose	291975	288983	1.01	0.829;1.30	0.910 (NS)

C_{max}, $AUC_{0-\tau}$ and $AUC_{0-\infty}$ expressed as geometric mean (ng/mL); t_{max} expressed as median (h).
*Difference (Female-Male).
95%CI = 95% Confidence Interval.
NS = Not significant.

No significant differences were found between female and male groups (young and elderly combined) concerning all BIA 2-194 pharmacokinetic parameters analyzed.

Overall Conclusions:

The kinetic profile of BIA 2-093 metabolites appeared to be independent of age and gender following single and multiple doses of 600 mg BIA 2-093.

Study 111: An open label, multiple-dose, single-centre study, investigating the pharmacokinetics of BIA 2-093 in subjects with moderate hepatic impairment.

Objectives:

- To characterize the pharmacokinetics (PK) of BIA 2-093 and its metabolites BIA 2-194, BIA 2-195, oxcarbazepine, BIA 2-093 glucuronide, BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide, after multiple oral doses (8 days) of BIA 2-093 in 2 groups of subjects: subjects with moderate hepatic impairment and healthy controls.
- To assess the relative safety and tolerability of BIA 2-093 in subjects with moderate hepatic impairment.

The study design is as follows:

Study Design	This was an open-label, multiple-dose, single-centre study, where BIA 2-093 (800 mg tablet) was administered to subjects with moderate hepatic impairment and to healthy controls, once daily, for 8 days.
Study Population	

		Height (cm)	Weight (kg)	BMI (kg/m^2)	Age (years)	Race	Gender
All subjects (N = 17)	Mean	169.5	63.27	22.01	42	Caucasian: 8 Coloured: 2 Black: 7	12 males, 5 females
	Range	156 – 187	49.2 – 91.1	16.4 – 28.4	18 – 60		
Hepatic impairment group (N = 9)	Mean	171.3	63.07	21.59	43.2	Caucasian: 4 Coloured: 1 Black: 4	6 males, 3 females
	Range	158 – 187	49.2 – 89.0	16.4 – 28.1	20 – 60		
Healthy control group (N = 8)	Mean	167.5	63.50	22.48	40.6	Caucasian: 4 Coloured: 1 Black: 3	6 males, 2 females
	Range	156 – 179	50.0 – 91.1	18.4 – 28.4	18 – 58		

To the extent possible, the healthy controls were to be demographically matched with respect to age, weight and gender.

Child Pugh scores:

Subject No.	Points scored					
	Encephalopathy Grade	Ascites	Serum bilirubin	Serum albumin	Prothrombin time	Total
1	1	2	2	3	1	9
3	1	1	3	2	1	8
5	1	2	3	2	1	9
7	1	1	3	2	1	8
9	1	2	2	3	1	9
11	1	1	3	1	1	7
13	1	2	3	1	1	8
15	1	3	1	2	1	8
17	1	2	3	1	1	8

Treatment Group	1. Moderate hepatic impairment based on Child Pugh Classification B (score 7-9) 2. Healthy

Dosage and Administration	Each subject was to receive an oral dose of 800 mg of BIA 2-093 daily for 8 consecutive days. Subjects returned to the clinic on each of Days 3, 4, 5, 6 and 7. Subjects were admitted to the research clinic again on the evening of Day 7 and were discharged on Day 9. The study medication was taken with 180 mL of water. The screening visit was performed 2 to 21 days before the first administration of study medication, the treatment phase consisted of 12 days (of which study medication was administered during the first 8 days), and the follow up visit was performed 15 to 19 days after the first administration of study medication. Batch number: 040122-L.
Sampling: Blood	For BIA 2-093 and metabolites: Day 1 to 7: 1, 2, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 7, 9, 12, 24, 72, 120 and 144 hours post dose Day 8: 1, 2, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 7, 9, 12, 24, 48, 72 and 96 hours post dose
Urine	For BIA 2-093 and metabolites: Days 1 to 7: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hours post dose Day 8: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hours post dose
Feces	none
Analysis	Lower Limits of Quantitation Plasma / Urine BIA 2-093 50 ng/ml / 50 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml / 50 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml / 50 ng/ml Oxcarbazepine 50 ng/ml / 50 ng/ml All glucuronides 50 ng/ml / 50 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 140, 400 and 800 and 2000 ng/ml for oxcarbazepine Inter-day precision: % CV: < 8.4 %for BIA 2-194 and BIA 2-195 <7.4 % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 95-104% for BIA 2-194 and BIA 2-195, 97-104% for BIA 2-093 and oxcarbazepine. Urine: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 140, 400 and 800 and 2000 ng/ml for oxcarbazepine

	Inter-day precision: % CV: < 8.7 %for BIA 2-194 and BIA 2-195 <7.6 % for BIA 2-093 and oxcarbazepine. Inter-day accuracy: 93.3-100.3% for BIA 2-194 and BIA 2-195, 97.4-102.1% for BIA 2-093 and oxcarbazepine Validation parameters for the glucuronides were also acceptable both in plasma and urine.
PK Assessment	Single Dose: AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, Steady State" AUCss, Cmaxss, Cmin ss, Tmax, t1/2, CLss/F, CLr, Vzss/F
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

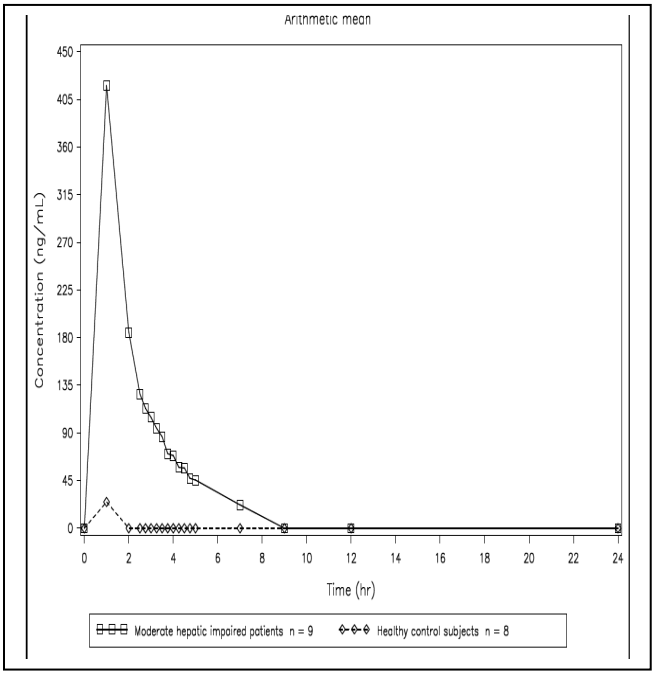
In plasma:

BIA 2-093 Plasma Concentrations

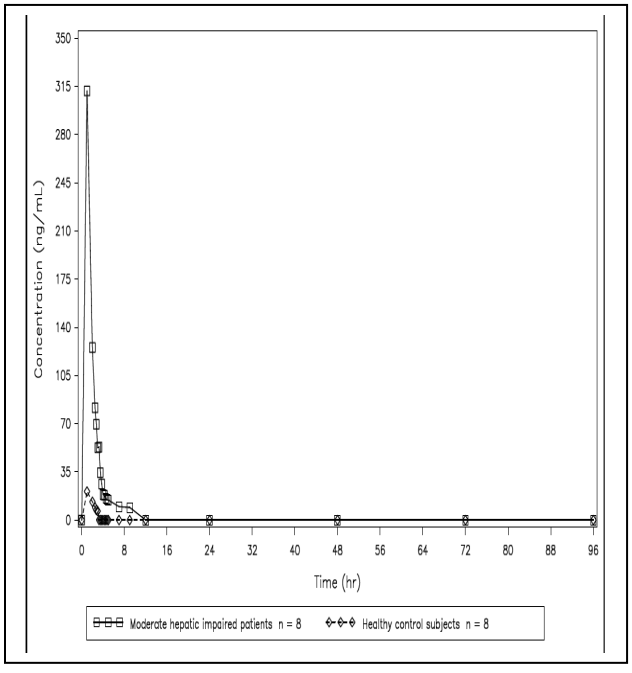
Almost all subjects in the healthy control group had BLQ plasma concentrations for BIA 2-093 at all time-points. The only measurable concentrations were at 1 hour after the first dose for Subjects 04 and 16, and from 1 to 3 hours after the last dose for Subject 04. In the hepatic impairment group, there were notably more subjects with measurable BIA 2-093 plasma concentrations.

The following 2 figures reflect the mean plasma BIA 2-093 concentrations on Day 1 and on Day 8:

Day 1



Day 8



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The higher concentrations in the hepatic impaired group on Day 1 and 8 is also reflected in the following Tables:

Table: Statistical Analysis for BIA 2-093 Pharmacokinetic Variables (Day 1)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
C_{max} *(ng/mL)*	2	91.32	8	318.78	349.06	(58.10 ; 2097.21)
$AUC_{(0\text{-}tlast)}$ *(h·ng/mL)*	2	45.66	8	521.03	1141.06	(94.78 ; 13736.63)
T_{max} ♣ *(h)*	2	1.00	8	1.00	p-value: 0.59	

♣ Medians, p-value according to Wilcoxon signed-ranked test

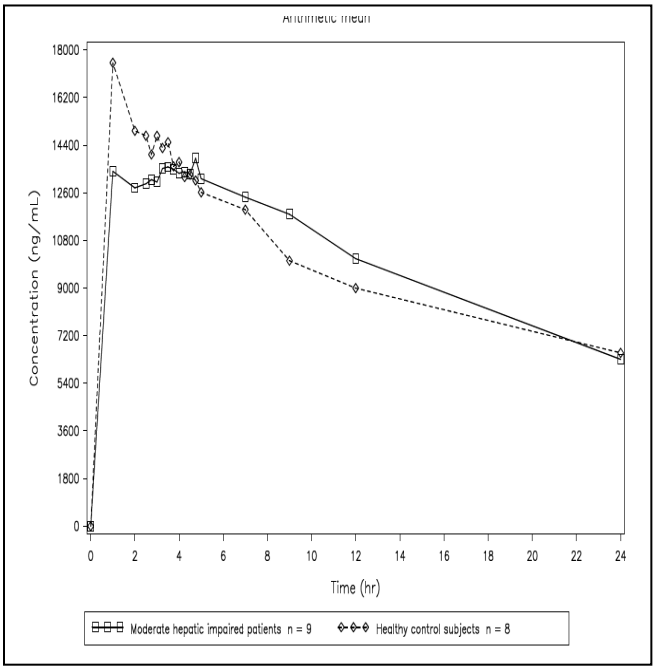
Table: Statistical Analysis for BIA 2-093 Pharmacokinetic Variables (Day 8)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
$C_{max,\ ss}$ *(ng/mL)*	1	166.00	6	398.91	240.31	(100.37 ; 575.36)
AUC_{ss} *(h·ng/mL)*	1	381.27	6	814.77	213.70	(68.20 ; 669.64)
$t_{½.z}$ *(h)*	1	1.163	6	1.25	107.69	(12.42 ; 933.76)

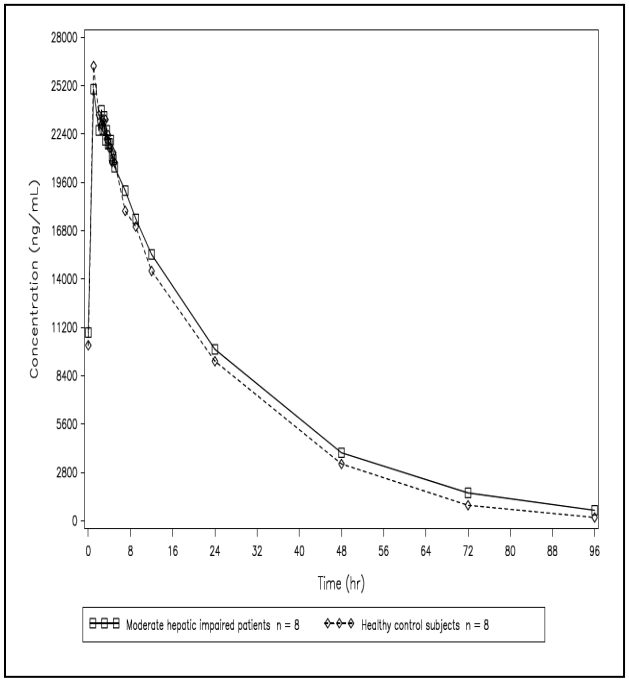
BIA 2-194 Plasma Concentrations

The following 2 figures reflect the mean plasma BIA 2-194 concentrations on Day 1 and on Day 8:

Day 1



Day 8



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The difference in the two groups is shown statistically in the following Tables:

Table: Statistical Analysis for BIA 2-194 Pharmacokinetic Variables (Day 1)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
C_{max} *(ng/mL)*	8	18079.92	9	16092.59	89.01	(75.04 ; 105.58)
$AUC_{(0\text{-}tlast)}$ *(h·ng/mL)*	8	232892.68	9	238792.73	102.53	(90.10 ; 116.69)
$AUC_{(0\text{-}\infty)}$ *(h·ng/mL)*	8	410520.21	9	409016.67	99.63	(78.10 ; 127.11)
$t_{½,z}$ *(h)*	8	18.49	9	17.18	92.91	(61.73 ; 139.83)
T_{max} ♣ *(h)*	8	1.00	9	2.75	p-value: 0.09	

Table Statistical Analysis for BIA 2-194 Pharmacokinetic Variables (Day 8)

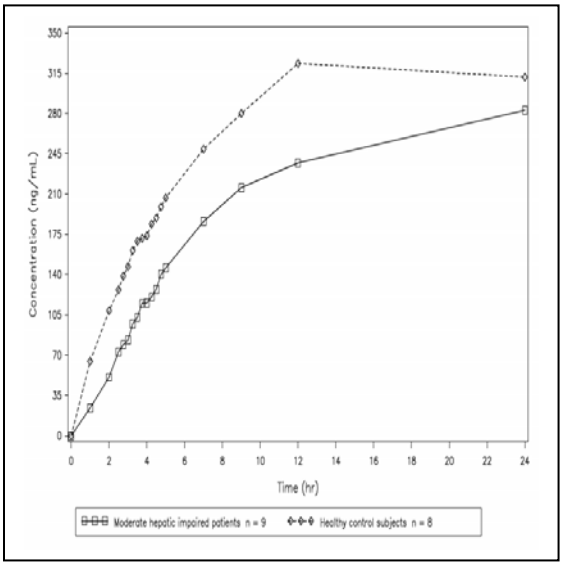
Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
$C_{max,\ ss}$ *(ng/mL)*	8	27219.24	8	25773.01	94.69	(75.92 ; 118.10)
$C_{min,\ ss}$ *(ng/mL)*	8	8786.21	8	8931.19	101.65	(67.89 ; 152.20)
AUC_{ss} *(h·ng/mL)*	8	368957.69	8	372854.28	101.06	(78.79 ; 129.62)
$t_{½,z}$ *(h)*	8	10.87	8	12.93	118.92	(78.54 ; 180.07)
CL_{ss}/F *(L/h)*	8	2.17	8	2.15	98.96	(77.15 ; 126.92)
$V_{z,\ ss}/F$ *(L)*	8	34.01	8	40.02	117.68	(92.01 ; 150.51)
$T_{max,\ ss}$ ♣ *(h)*	8	1.00	8	1.75	p-value: 0.86	
$CL_{r,\ ss}$ *(mL/h)*	8	1388.35	8	1333.91	96.08	(71.06 ; 129.90)

No major differences were seen in the hepatic impaired compared to the healthy subjects. Due to the low extent of eslicarbazepine plasma protein-binding, changes in binding due to impaired hepatic function were expected to be small.

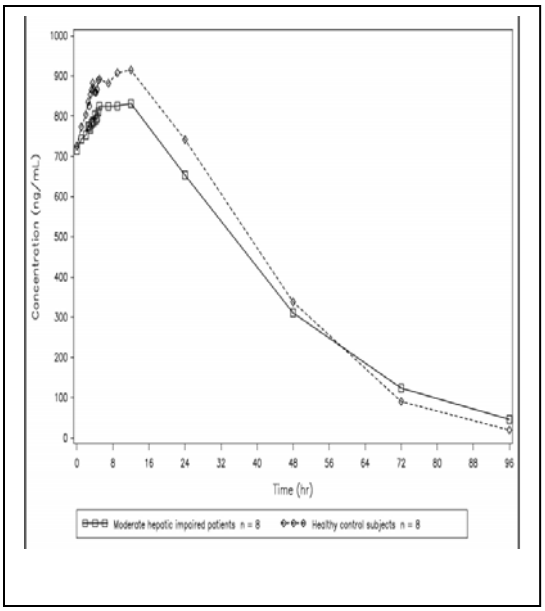
BIA 2-195 Plasma Concentrations

The following 2 figures reflect the mean plasma BIA 2-195 concentrations on Day 1 and on Day 8:

Day 1



Day 8



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The difference in the two groups is shown statistically in the following Tables:

Table: Statistical Analysis for BIA 2-195 Pharmacokinetic Variables (Day 1)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
C_{max} *(ng/mL)*	8	335.18	9	285.02	85.04	(63.40 ; 114.06)
$AUC_{(0\text{-tlast})}$ *(h·ng/mL)*	8	6107.54	9	4584.92	75.07	(54.12 ; 104.13)
T_{max} ♣ *(h)*	8	12.00	9	23.92	p-value: 0.06	

♣ Medians, p-value according to Wilcoxon signed ranked test

Table Statistical Analysis for BIA 2-195 Pharmacokinetic Variables (Day 8)

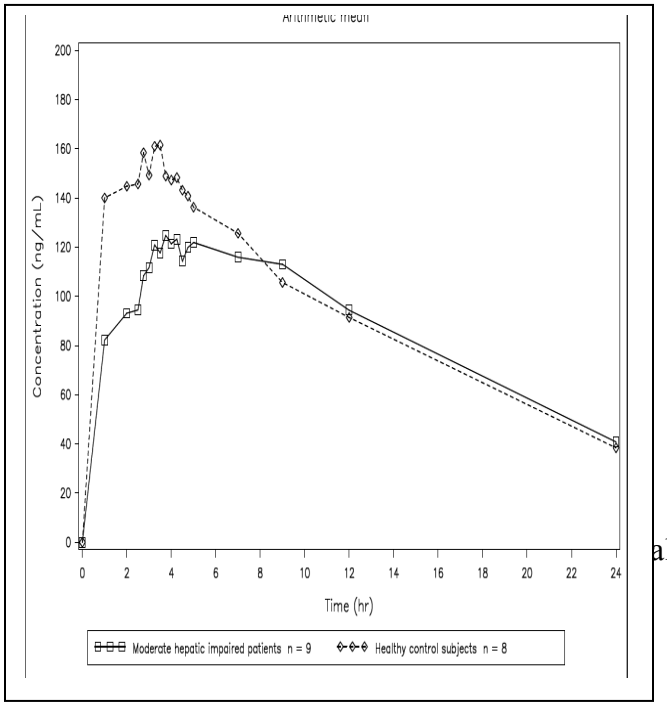
Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
$C_{max, ss}$ *(ng/mL)*	8	923.78	8	787.11	85.20	(59.71 ; 121.58)
$C_{min, ss}$ *(ng/mL)*	8	690.39	8	580.59	84.10	(54.81 ; 129.03)
AUC_{ss} *(h·ng/mL)*	8	19907.05	8	17028.38	85.54	(59.15 ; 123.71)
$t_{½.z}$ *(h)*	8	18.25	8	17.42	95.45	(72.25 ; 126.08)
CL_{ss}/F *(L/h)*	8	40.19	8	46.98	116.90	(80.83 ; 169.07)
$V_{z, ss}/F$ *(L)*	8	1058.17	8	1180.71	111.58	(72.74 ; 171.15)
$T_{max, ss}$ ♣ *(h)*	8	9.50	8	8.00	p-value: 0.87	
$CL_{r, ss}$ *(mL/h)*	8	1592.14	8	1426.46	89.59	(64.87 ; 123.74)

♣ Medians, p-value according to Wilcoxon signed ranked test

No major differences were seen in the hepatic impaired compared to the healthy subjects.

Oxcarbazepine Plasma Concentrations

The following 2 figures reflect the mean plasma oxcarbazepine concentrations on Day 1 and on Day 8:



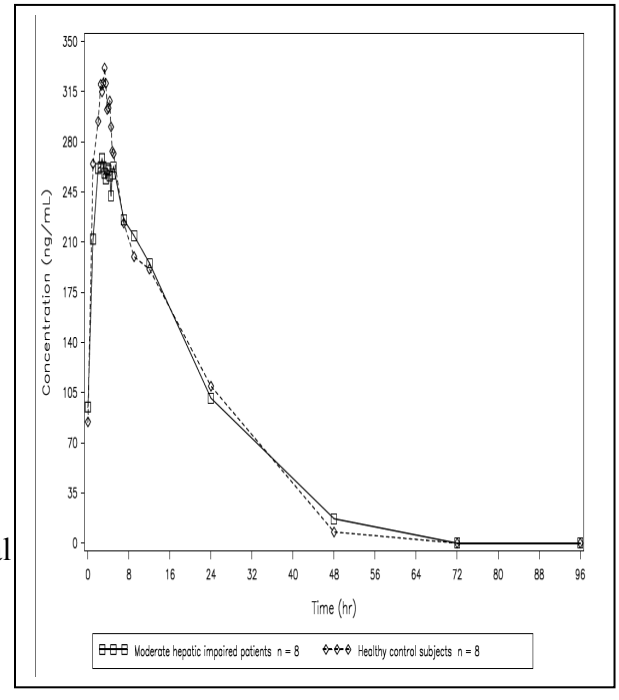


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Table Statistical Analysis for Oxcarbazepine Pharmacokinetic Variables (Day 1)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
C_{max} *(ng/mL)*	8	173.19	9	137.91	79.63	(55.19 ; 114.88)
$AUC_{(0\text{-}tlast)}$ *(h·ng/mL)*	8	1865.40	9	1685.11	90.33	(55.44 ; 147.20)
$AUC_{(0\text{-}\infty)}$ *(h·ng/mL)*	8	3608.30	9	4547.10	126.02	(74.40 ; 213.44)
$t_{½,z}$ *(h)*	8	14.72	9	22.87	155.39	(80.27 ; 300.80)
T_{max}♣ *(h)*	8	3.38	9	3.75	p-value: 0.19	

Table 11-9 Statistical Analysis for Oxcarbazepine Pharmacokinetic Variables (Day 8)

Variable	Healthy control group		Moderate hepatic impairment group		%ratio (impaired /control)	95% CI of ratio
	n	LSMean	n	LSMean		
$C_{max,\ ss}$ *(ng/mL)*	8	338.64	8	284.59	84.04	(60.23 ; 117.26)
$C_{min,\ ss}$ *(ng/mL)*	8	89.43	8	96.73	108.17	(70.87 ; 165.09)
AUC_{ss} *(h·ng/mL)*	8	4516.35	8	4283.74	94.85	(68.11 ; 132.10)
$t_{½,z}$ *(h)*	8	16.76	8	14.18	84.63	(65.00 ; 110.18)
CL_{ss}/F *(L/h)*	8	177.13	8	186.75	105.43	(75.70 ; 146.83)
$V_{z,\ ss}/F$ *(L)*	8	4282.22	8	3820.65	89.22	(57.30 ; 138.93)
$T_{max,\ ss}$♣ *(h)*	8	2.88	8	3.25	p-value: 0.44	
$CL_{r,\ ss}$ *(mL/h)*	8	83.11	8	130.62	157.17	(99.76 ; 247.62)

No major differences were seen in the hepatic impaired compared to the healthy subjects.

BIA 2-093 Glucuronide Plasma Concentrations

In the hepatic impaired group some subjects had measurable plasma concentration of BIA 2-093 glucuronide at some time points on Day 1 and 8.

In the healthy group, only 1 subject had measurable plasma concentration on day 1 and all other were BLQ.

BIA 2-194 Glucuronide Plasma Concentrations

Mean BIA 2-194 glucuronide plasma concentrations were higher in the hepatic impaired group than in the healthy control group.

BIA 2-195 Glucuronide Plasma Concentrations

Mean BIA 2-195 glucuronide plasma concentrations were higher in the healthy control

group than in the hepatic impaired group for most of the time-points.

Oxcarbazepine Glucuronide Plasma Concentrations

Mean oxcarbazepine glucuronide plasma concentrations were higher in the healthy control group than in the hepatic impaired group until 12 hours post-dose on Day 1, whereafter it was higher in the hepatic impaired group for most of the rest of the time-points.

Urine Concentrations

BIA 2-093 Urine Concentrations

Mean BIA 2-093 urine concentrations were higher in the subjects with moderate hepatic impairment than in the healthy control group up to 96 hours after the first dose (Day 5). Pre-dose on Day 8, the mean BIA 2-093 urine concentration was higher in the healthy control group than in the hepatic impairment group, and for the first 4 hours post-dose on Day 8 it was higher in the hepatic impairment group. From 4 hours post-dose on Day 8, the mean BIA 2-093 urine concentrations were similar between the 2 groups.

BIA 2-194 Urine Concentrations

On Day 1, it was not clear whether the healthy or the hepatic impaired group had higher concentration. At some collection intervals, the healthy group had higher concentration, whereas in the others the hepatic group had higher concentrations. For all the time intervals from pre-dose on Day 8 until 72 hours after the last dose the BIA 2-194 mean urine concentrations were higher in the healthy control group than in the hepatic impairment group. During the last collection interval, the BIA 2-194 mean urine concentration was higher in the hepatic impairment group than in the healthy control group.

BIA 2-195 Urine Concentrations

For most intervals BIA 2-195 mean urine concentrations were higher in the healthy control group than in the hepatic impairment group.

Oxcarbazepine Urine Concentrations

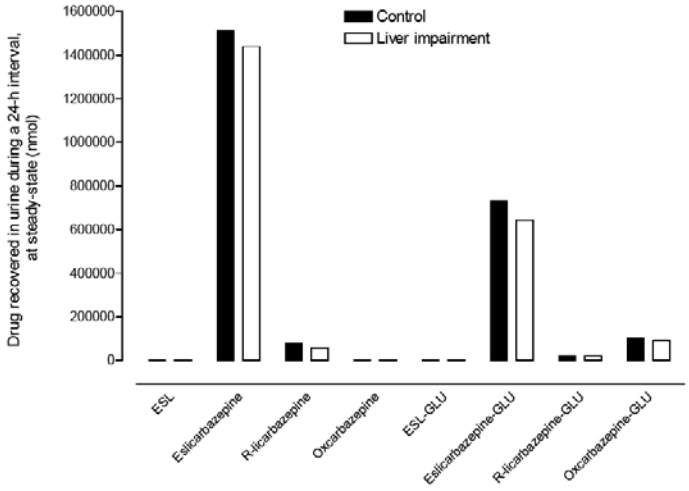
No trend could be observed in the oxcarbazepine mean urine concentrations: for some time intervals it was higher in the hepatic impairment group, and for others higher in the healthy control group.

BIA 2-093, BIA 2-194 and BIA 2-195 Glucurnonides:

Generally these were higher in the healthy group compared to the hepatic impaired group.

The mean urinary recoveries of the glucuronides are shown in the following figure:

Figure: Mean Cumulative Urinary Excretion (in nmol) of SEP-0002093 and its Metabolites in Urine Collected During a 24-Hour Interval on Day 8 (n=8 per group)



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Overall Conclusions:

- In the hepatic impaired group, inhibition of the hepatic metabolism of the parent drug, **BIA 2-093**, in the group with hepatic impairment was evident. Most of the healthy control group of 8 subjects had BLQ plasma concentrations for BIA 2-093 at all timepoints. In the hepatic impairment group of 9 subjects, there were notably more subjects with measurable BIA 2-093 plasma concentrations, but systemic exposure to BIA 2-093 was about 0.01% of systemic exposure to BIA 2-194 and, therefore, it is not expected that BIA 2-093 will have a significant contribution to the therapeutic effects.
- For **BIA 2-194**, no statistically significant difference was found between the hepatic impaired group and the healthy control group regarding any of the PK parameters assessed, at Day 1 or at Day 8. Mean ratios (impaired/control) for Cmax and the AUC variables of BIA 2-194 ranged between 89.01% and 102.53% on Day 1 and between 94.69% and 101.06% on Day 8. No statistically significant difference on the rate or extent of formation of **BIA 2-194 glucuronide** was found at Day 1 or Day 8 between the control and moderate liver impairment groups. Extent of systemic exposure to BIA 2-194 glucuronide corresponded approximately to 2%-3% of exposure to BIA 2-194, in both groups. Urine excretion of BIA 2-194 and BIA 2-194 glucuronide was similar between liver impaired and healthy subjects, and the amount of BIA 2-194 recovered in urine in the unchanged form was approximately 2-fold higher than the amount recovered in the glucuronide form.

- For **BIA 2-195**, no statistically significant difference was found between the hepatic impaired group and the healthy control group regarding the rate and extent of its formation. The mean ratios (impaired/control) for Cmax and the AUC variables for BIA 2-195 ranged between 75.07% and 85.54% on Day 1 and between 85.20% and 84.10% on Day 8. Extent of systemic exposure to **BIA 2-195 glucuronide** was approximately 3% of exposure to BIA 2-195, in both groups. Urine excretion of BIA 2- 195 and BIA 2-195 glucuronide was similar between liver impaired and healthy subjects, and the amount of BIA 2-195 recovered in urine in the unchanged form was approximately 3-fold or 4-fold lower than the amount recovered in the glucuronide form.
- For **oxcarbazepine**, the results indicate no statistically significant difference between the hepatic impaired group and the healthy control group regarding the rate and extent of its formation. The mean ratios (impaired/control) for Cmax, AUC(0-tlast) and AUC(0-∞) for oxcarbazepine on Day 1 were 79.63%, 90.33% and 126.02%, respectively. On Day 8, the mean ratios (impaired/control) for Cmax, ss and AUCss for oxcarbazepine were 84.04% and 94.85, respectively. Urine excretion of oxcarbazepine and oxcarbazepine glucuronide was similar in liver impaired and healthy subjects, and the amount of oxcarbazepine recovered in urine in the unchanged form was much lower (~ 2%) than the amount recovered in the glucuronide form.
- Altogether, the results showed that BIA 2-093 is rapidly and extensively hydrolyzed to BIA 2-194, its major circulating metabolite. In liver impaired subjects, there was a higher amount of parent drug (BIA 2-093) that passes the liver without undergoing significant first-pass metabolism, but it was metabolized by the liver during subsequent liver passages or excreted in urine in the unchanged form. Systemic exposure to BIA 2-093 was about 0.01% of systemic exposure to BIA 2-194 and, therefore, it is not expected that BIA 2-093 will have a significant contribution to the therapeutic effects. BIA 2-194 was the predominant metabolite and showed to be excreted in urine in the unchanged (~ 2/3) and glucuronide (~ 1/3) forms. Using AUCss as a measure of systemic exposure, BIA 2-194 corresponded to approximately 91% of the sum of all circulating drug entities and to approximately 94% of the sum of the active compounds (BIA 2-093 + BIA 2-194 + BIA 2-195 + oxcarbazepine), both in liver impaired patients and control healthy subjects. Minor active metabolites were BIA 2-195 and oxcarbazepine, corresponding respectively to 5% and 1% of exposure to circulating active entities. The sum of plasma glucuronides (BIA 2-093 glucuronide + BIA 2-194 glucuronide + BIA 2-195 glucuronide + oxcarbazepine glucuronide) corresponded to approximately 4% of total exposure (inactive plus active entities) in liver impaired subjects and to approximately 3% of total exposure in control subjects. There were no significant differences between liver impaired and control group subjects in the oxcarbazepine PK nor in the BIA 2-194, BIA 2-195 and oxcarbazepine glucuronides PK, suggesting that formation of oxcarbazepine and glucuronidation of BIA 2-194, BIA 2-195 and oxcarbazepine are not significantly affected by moderate liver impairment.

Study 112: An open label, single-dose, single-center study, investigating the pharmacokinetics of BIA 2-093 in subjects with various degrees of renal impairment.

Objectives:

- To characterize the pharmacokinetics (PK) of BIA 2-093 and its metabolites in 5 different groups of subjects with various degrees of renal function, including subjects requiring hemodialysis.
- To assess the relative safety and tolerability of BIA 2-093 in subjects with impaired renal function.

The study design is as follows:

<table>
<tr><td>Study Design</td><td>This was an open-label, single-dose, single-centre study in five groups of subjects with various degrees of renal function (based on creatinine clearance). The trial consisted of a screening visit, a treatment phase and a follow-up visit. All subjects were to be treated with a single oral dose of BIA 2-093. Blood and urine samples were collected for the PK analysis, and safety assessments were performed.</td></tr>
<tr><td>Study Population</td><td>
<table>
<tr><th></th><th></th><th>Height (cm)</th><th>Weight (kg)</th><th>BMI (kg/m^2)</th><th>Age (years)</th><th>Race</th><th>Gender</th></tr>
<tr><td rowspan="2">All subjects (N = 40)</td><td>Mean</td><td>169.9</td><td>72.07</td><td>24.96</td><td>42.2</td><td rowspan="2">Caucasian: 19
Coloured: 2
Black: 19</td><td rowspan="2">26 males,
14 females</td></tr>
<tr><td>Range</td><td>152 – 190</td><td>50.1 – 103.6</td><td>17.9 – 32.7</td><td>21 – 66</td></tr>
<tr><td rowspan="2">Normal renal function group (N = 8)</td><td>Mean</td><td>177.8</td><td>78.36</td><td>24.61</td><td>29.8</td><td rowspan="2">Caucasian: 8</td><td rowspan="2">7 males,
1 female</td></tr>
<tr><td>Range</td><td>154 – 190</td><td>54.2 – 98.6</td><td>21.9 – 28.5</td><td>21 – 35</td></tr>
<tr><td rowspan="2">Mild renal impairment group (N = 8)</td><td>Mean</td><td>166.1</td><td>71.84</td><td>25.96</td><td>56.0</td><td rowspan="2">Caucasian: 8</td><td rowspan="2">1 male,
7 females</td></tr>
<tr><td>Range</td><td>159 – 181</td><td>64.2 – 95.0</td><td>22.6 – 29.0</td><td>49 – 65</td></tr>
<tr><td rowspan="2">Moderate renal impairment group (N = 8)</td><td>Mean</td><td>169.9</td><td>76.15</td><td>23.46</td><td>40.6</td><td rowspan="2">Caucasian: 2
Coloured: 2
Black: 4</td><td rowspan="2">6 males,
2 females</td></tr>
<tr><td>Range</td><td>155 – 182</td><td>55.5 – 103.6</td><td>18.8 – 32.1</td><td>23 – 66</td></tr>
<tr><td rowspan="2">Severe renal impairment group (N = 8)</td><td>Mean</td><td>169.8</td><td>69.23</td><td>24.10</td><td>45.4</td><td rowspan="2">Black: 8</td><td rowspan="2">7 males,
1 female</td></tr>
<tr><td>Range</td><td>156 – 179</td><td>50.1 – 87.0</td><td>17.9 – 32.7</td><td>28 – 59</td></tr>
<tr><td rowspan="2">End stage renal disease group (N = 8)</td><td>Mean</td><td>165.9</td><td>64.76</td><td>23.65</td><td>39.3</td><td rowspan="2">Caucasian: 1
Black: 7</td><td rowspan="2">5 males,
3 females</td></tr>
<tr><td>Range</td><td>152 – 180</td><td>53.9 – 81.2</td><td>20.5 – 29.1</td><td>29 – 49</td></tr>
</table>
</td></tr>
<tr><td>Treatment Group</td><td>The groups were as follows:
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 (ESRD) requiring haemodialysis.</td></tr>
<tr><td>Dosage and Administration</td><td>The trial consisted of three trial periods:
_ Trial period 1 (a screening visit)
_ Trial period 2 (treatment phase)
_ Trial period 3 (follow-up visit).
The trial commenced with a screening visit (Visit 1) at 2 to 21 days before dose administration to assess subject eligibility</td></tr>
</table>

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	The Treatment phase (Visits 2 to 6) commenced with subjects being admitted to the research clinic the evening before the day of dosing (Visit 2, Day -1). Each subject received a single, 800 mg oral dose of BIA 2-093 the following morning (Day 1), which marked the beginning of the Profile period. Subjects were discharged on Day 2 and returned to the clinic for further sampling on Days 3 (Visit 4), 4 (Visit 5) and 5 (Visit 6). A final safety assessment was performed 3 to 7 days after completion of the Treatment phase during a Follow-up visit (Visit 7). For the dialysis group, dosing was done the day before dialysis and this marked the beginning of the Profile period. Routine dialysis was given 12-18 hours after dosing, and profiling continued during dialysis. The subjects were discharged after dialysis, and returned to the research clinic the following day (Visit 3, Day 3) for profiling and a safety assessment. During their next dialysis session (Visit 4, Day 4), their sampling was done during the dialysis session and regular safety assessments were performed. This marked the end of the Treatment phase. BIA 2-093, 800 mg tablet, was administered per os (orally) with 180 mL of water. Batch number: 040122-L.
Sampling: Blood	For BIA 2-093 and metabolites: Gr 1-4: 1, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 5, 7, 9, 12, 24, 48, 72 and 96 hours post dose Gr 5: 1, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 5, 7, 9, 12*, 36 and 60* hours post dose *Blood PK samples included pre- and post-dialysis samples, as well as dialysate and pre- and post-filter blood samples, collected at the first hour and third hour of dialysis
Urine	For BIA 2-093 and metabolites: Gr 1-4: 1: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and hours post dose Gr 5: 0-4, 4-8, 8-12, 12-36 and 36-72 (if obtainable)
Feces	none
Analysis	Lower Limits of Quantitation Plasma / Urine BIA 2-093 50 ng/ml 50 ng/ml BIA 2-194 (S-licarbazepine) 50 ng/ml 50 ng/ml BIA 2-195 (R-licarbazepine) 50 ng/ml 50 ng/ml Oxcarbazepine 50 ng/ml 50 ng/ml All glucuronides 50 ng/ml 50 ng/ml Plasma: Method: LC/MS/MS method Linear Range: 50 – 1000 ng/mL for eslicarbazepine acetate and oxcarbazepine and 50 – 25000 ng/mL for BIA 2-194 (S-licarbazepine) and BIA 2-195 (R-licarbazepine). Quality control concentrations: 50, 140, 10000, 20000 ng/ml for BIA 2-194 and BIA 2-195; 50 and their glucuronides, 140,

	400 and 800 and 2000 ng/ml for oxcarbazepine Inter-day precision: % CV: < 11.4 %for BIA 2-194 and BIA 2-195 <3.1 % for BIA 2-093 and oxcarbazepine and their glucurnonides. Inter-day accuracy: 89.9-109.1% for BIA 2-194 and BIA 2-195, 92.6-107.9% for BIA 2-093 and oxcarbazepine. Validation parameters for the glucuronides were also acceptable.
PK Assessment	Single Dose: AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, CL/F, CLr, Vz/F
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Pharmacokinetic Results:

In plasma:

BIA 2-093 Plasma Concentrations

All subjects with normal renal function and mild renal impairment had BLQ values at all time points. In the other groups, 1-3 subjects had measurable concentrations of one time point.

The Pharmacokinetic parameters are shown in the following Table:

Table: Geometric Mean (SD) BIA 2-093 Pharmacokinetic Variables

Variable (unit)	Normal renal function group		Mild renal impairment group		Moderate renal impairment group		Severe renal impairment group		ESRD	
	n	Geometric Mean (SD)	n	Geometric Mean (SD)	n	Geometric Mean (SD)	n	Geometric Mean (SD)	n	Geometric Mean (SD)
C_{max} (ng/mL)					1	68.500	3	73.015 (15.174)	1	53.000
T_{max} (hr)					1	1.000	3	1.000 (0.000)	1	1.000
AUC(0-12h) (hr·ng/mL)										
AUC(0-t_{last}) (hr·ng/mL)					1	34.250	3	36.507 (7.857)	1	26.500
AUC(0-∞) (hr·ng/mL)										
$t_{½,z}$ (hr)										
CL/F (l/hr)										
V_z/F (L)										
CL_R (mL/h)										

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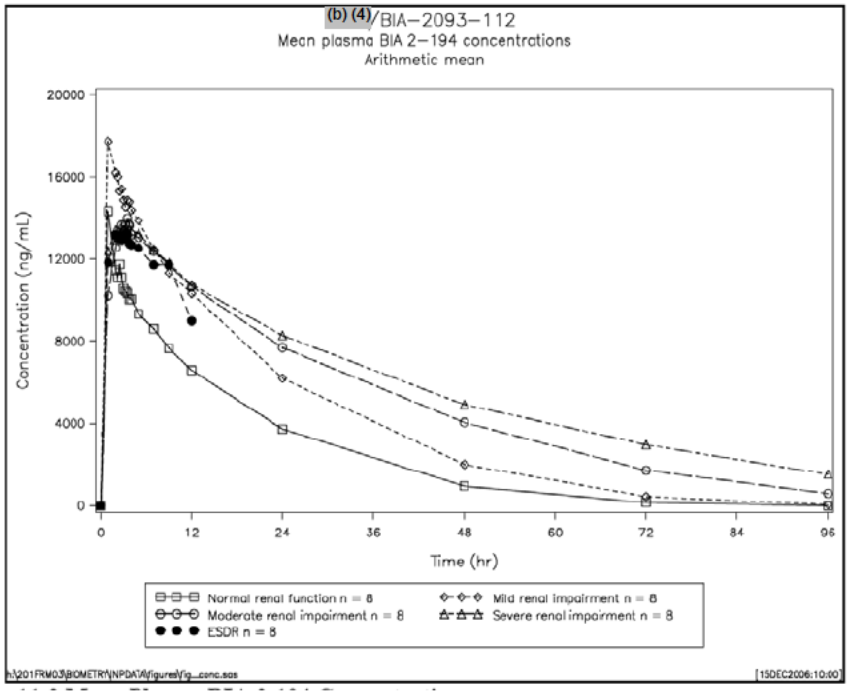
- BIA 2-093 showed to present an extensive first-pass metabolism that resulted in no measurable BIA 2-093 plasma concentrations.

BIA 2-194 Plasma Concentrations

The renal impaired patients had higher concentrations than the healthy group, as seen in the Figure below:



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The Pharmacokinetic parameters are shown in the following Table for Group 5 and 1,2,3 and 4:

Table Statistical Analysis for BIA 2-194 Pharmacokinetic Variables (Group 5 / Group 1)

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

Table Statistical Analysis for BIA 2-194 Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

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	

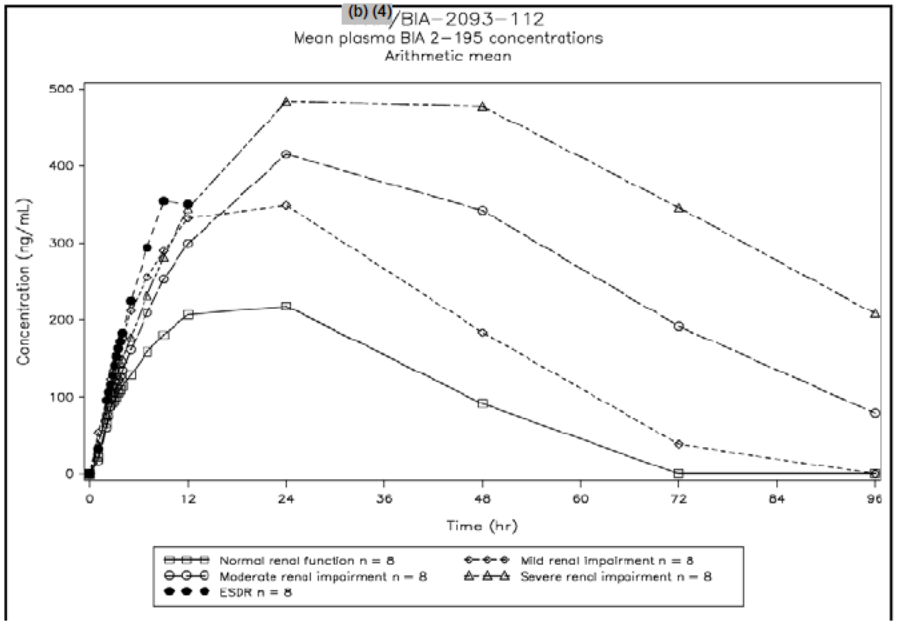
♠ Medians, p-value according to Wilcoxon signed rank test

This metabolite represents 95% of the total exposure to the drug.

- AUC(0-12h): no clear relationship between this variable and the degree of renal impairment was evident. However, the AUC(0-12) and AUC for the ESRD group were similar as expected, since dialysis was performed 12 hours after administration of medication.
- AUC (tlast) and AUC(0-∞): for both these variables a clear tendency to increase with increasing degrees of renal impairment was present. As expected, AUC(tlast) was similar to AUC(0-12) in the ESRD group, since dialysis was performed 12 hours after administration of dosing. In relation to the normal function group, AUC(tlast) and AUC(0-∞) significantly increased respectively 62% and 61% in the mild renal impairment group, 106% and 111% in the moderate renal impairment group, and 131% and 154% in the severe renal impairment group.
- CL/F: there was a clear tendency for this parameter to decreased by 38, 53 and 61% respectively, with increasing renal impairment. This is to be expected since the AUC and clearance are inversely proportional. The decrease was significant for all renal impairment degrees.
- T1/2: terminal elimination half-life significantly increased in the moderate and severe renal impairment groups (18, 28 hr, respectively) relative to the normal function and mild impairment groups (11 hrs).
- Vz: volume of distribution is proportional to clearance. However, no clear relationship between this parameter and degree of renal impairment could be discerned. The reason is probably the effect of renal impairment on body fluid distribution.
- Cmax: maximum plasma concentrations did not seem to be affected by the various degrees of renal impairment. The reason for the rather high value (geometric mean) of 18677 ng/mL for the mild renal impairment group is not clear.
- Tmax: time to maximum concentrations significantly increased in the moderate and severe renal impairment groups (3 hr) relative to the normal function group and mild renal impairment group (1 hr).
- CLR: Renal clearance significantly decreased with increasing degrees of renal impairment.
- The total amount of BIA 2-194 recovered in urine from time of dosing until 72 h post-dose was similar in the control and mild renal impairment groups (247.6 mg and 238.2 mg, respectively). However, a marked decrease in the total amount of BIA 2-194 recovered in urine was found in the moderate and severe renal impairment groups (respectively, 113.7 mg and 57.8 mg, which corresponds to a reduction of respectively 54% and 77% in relation to the control group).

BIA 2-195 Plasma Concentrations

Similarly higher concentrations were seen in the renal impaired groups



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The Pharmacokinetic parameters are shown in the following Table. No evaluable statistical data for plasma BIA 2-195 were available for Group 5 / Group 1.

Table: Statistical Analysis for BIA 2-195 Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

Variable (unit)	Normal renal function group		Mild renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean			n	LSMean			n	LSMean		
C_{max} (ng/mL)	8	211.076	8	348.843	165.27	(124.59 ; 219.24)	8	410.828	194.63	(146.72 ; 258.19)	8	465.928	220.74	(166.40 ; 292.82)
AUC(0-12h) (hr·ng/mL)	8	1522.370	8	2435.245	159.96	(117.92 ; 217.00)	8	2025.731	133.06	(98.09 ; 180.51)	8	2157.860	141.74	(104.49 ; 192.28)
AUC(0-t_{last}) (hr·ng/mL)	8	7583.916	8	14257.084	187.99	(139.83 ; 252.73)	8	24449.594	322.39	(239.80 ; 433.41)	8	33151.064	437.12	(325.15 ; 587.66)
AUC(0-∞) (hr·ng/mL)	1	14448.342	6	19613.758	135.75	(65.93 ; 279.52)	8	28315.970	195.98	(96.43 ; 398.32)	8	44942.919	311.06	(153.05 ; 632.21)
$t_{½,z}$ (hr)	1	33.112	6	24.469	73.90	(35.51 ; 153.78)	8	24.728	74.68	(36.36 ; 153.37)	8	39.066	117.98	(57.45 ; 242.30)
Cl/F (l/hr)	1	55.370	6	40.788	73.66	(35.77 ; 151.68)	8	28.253	28.253	(25.10 ; 103.71)	8	17.800	32.15	(15.82 ; 65.34)
V_z/F (L)	1	2645.052	6	1439.855	54.44	(27.21 ; 108.92)	8	1007.908	1007.908	(19.28 ; 75.30)	8	1003.233	37.93	(19.19 ; 74.95)
CL_R *(mL/h)*	1	524.086	6	562.699	103.37	(49.95 ; 230.79)	8	221.968	42.35	(19.98 ; 89.79)	8	88.173	16.82	(7.94 ; 35.67)
T_{max} (hr)♠	8	24.000	8	24.000	p-value: 1.0000		8	24.000	p-value: 0.2207		8	36.107	p-value: 0.0218	

♠ Medians, p-value according to Wilcoxon signed rank test

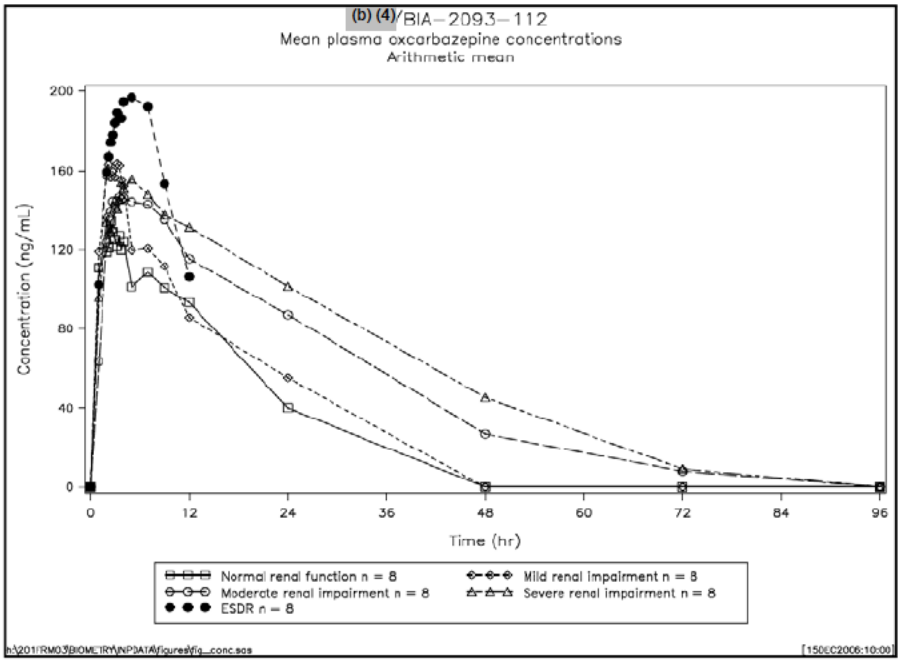
Reviewer's Comment: The calculations of mean AUC0-∞ is not reliable in this case for the normal group, as it was based on only one subject and was not reportable for the rest. Hence mean ratio's for the impaired/control group should be based on AUC0-last

This metabolite represents less than 5% of the total exposure of the drug.

- AUC(0-12h): no clear relationship between this variable and the degree of renal impairment was evident. However, the AUC(0-12h) and AUC for the ESRD group were similar as expected, since dialysis was performed 12 hours after administration of medication.
- AUC (tlast) and AUC(0-∞): for both these variables a clear tendency to increase with increasing degrees of renal impairment was present.
- CL/F: there was a clear tendency for clearance to decrease with increasing renal impairment. This is to be expected since the AUC and clearance are inversely proportional.
- t½.z: no clear relationship between half-life and the degree of renal impairment groups was observed.
- Vz: A tendency for volume of distribution to decrease with increasing renal impairment was discerned. This is in line with the findings for clearance which is proportional to the volume of distribution.
- Cmax: maximum plasma concentrations increased with increased renal impairment. This could be ascribed to slower metabolism by the liver in patients with decreased renal function.
- Tmax: no clear relationship between time to maximum concentration and the degree of renal impairment was observed. .
- CLR: renal clearance significantly decreased in the moderate and severe renal impairment groups; an unexpected high value found for the mild renal impairment group is difficult to explain.

Oxcarbazepine Plasma Concentrations

Higher concentrations were seen in the renal impaired groups



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The Pharmacokinetic parameters are shown in the following Tables.

Table: Statistical Analysis for Oxcarbazepine Pharmacokinetic Variables (Group 5 / Group 1)

Variable	Normal renal function group (n = 8)		ESRD		%Ratio (Impaired/Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean		
C_{max} (ng/mL)	8	138.339	8	208.473	150.70	(117.18 ; 193.80)
AUC(0-12h) (hr·ng/mL)	8	1218.276	8	1832.298	150.40	(116.68 ; 193.87)
AUC(0-t_{last})	8	1725.347	8	1832.298	106.20	(66.23 ; 170.29)
AUC(0-∞) (hr·ng/mL)	7	3404.323	8	3038.797	89.26	(57.23 ; 139.23)
$t_{½,z}$ (hr)	7	16.013	8	7.281	45.47	(27.82 ; 74.31)
CL/F (l/hr)	7	234.995	8	263.262	112.03	(71.83 ; 174.73)
V_z/F (L)	7	5428.792	8	2765.568	50.94	(37.32 ; 69.54)
CL_R *(mL/h)*	7	45.843	4	3.840	8.38	(4.71 ; 14.89)
T_{max} (hr)♠	8	2.500	8	3.767	p-value 0.0251	

♠ Medians, p-value according to Wilcoxon signed rank test

Table: Statistical Analysis for Oxcarbazepine Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

Variable (unit)	Normal renal function group		Mild renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean			n	LSMean			n	LSMean		
C_{max} (ng/mL)	8	138.339	8	172.293	124.54	(96.85 ; 160.16)	8	157.629	113.94	(88.60 ; 146.53)	8	157.955	114.18	(88.79 ; 146.83)
AUC(0-12h) (hr·ng/mL)	8	1218.276	8	1388.146	113.94	(88.40 ; 146.88)	8	1460.113	119.85	(92.98 ; 154.49)	8	1496.463	122.83	(95.29 ; 158.34)
AUC(0-t_{last}) (hr·ng/mL)	8	1725.347	8	2155.450	124.93	(77.91 ; 200.33)	8	3115.840	180.59	(112.62 ; 289.59)	8	4005.211	232.14	(144.77 ; 372.25)
AUC(0-∞) (hr·ng/mL)	7	3404.323	8	3642.803	107.01	(68.61 ; 166.90)	8	5868.177	172.37	(110.52 ; 268.86)	7	6909.980	202.98	(128.25 ; 321.24)
$t_{½,z}$ (hr)	7	16.013	8	15.628	97.60	(59.72 ; 159.50)	8	23.824	148.78	(91.04 ; 243.14)	7	27.285	170.39	(102.60 ; 282.98)
CLl/F (l/hr)	7	234.995	8	219.611	93.45	(59.92 ; 145.76)	8	136.329	58.01	(37.19 ; 90.48)	7	115.775	49.27	(31.13 ; 77.97)
V_z/F (L)	7	5428.792	8	4951.554	91.21	(66.82 ; 124.50)	8	4685.714	86.31	(63.23 ; 117.82)	7	4557.346	83.95	(60.88 ; 115.76)
CL_R (mL/h)	7	45.843	8	56.726	123.74	(76.96 ; 198.96)	8	30.206	65.89	(40.98 ; 105.94)	7	32.392	70.66	(43.27 ; 115.39)
T_{max} (hr)♣	8	2.500	8	2.500	p-value: 0.9585		8	3.250	p-value: 0.0631		8	5.000	p-value: 0.0251	

♣ Medians, p-value according to Wilcoxon signed rank test

Reviewer's Comment: Fraction extrapolated in the calculations of AUC0-inf is very high, hence does not appear reliable.

This metabolite represents 1% of the total exposure of the drug.

- AUC(0-12h): a gradual, although not significant, increase in this variable was observed associated with increased renal impairment.
- AUC (tlast) and AUC(0-∞): for both these variables a clear tendency to increase with increasing degrees of renal impairment was present.
- CL/F: there was a clear tendency for clearance to decrease with increasing renal impairment. This is to be expected since the AUC and clearance are inversely proportional.
- t½.z: greatly prolonged half-lives were associated with moderate and severe renal failure.
- Vz: volume of distribution tended to decrease with increasing renal impairment. Changes in body fluid distribution caused by renal impairment could be the reason for this finding.
- Cmax: no relationship between maximal plasma concentrations and degrees of renal impairment was observed.
- Tmax: time to maximum concentrations was significantly elevated in the severe renal impairment group.
- CLR: renal clearance tended to decrease in the moderate and severe renal impairment groups.

BIA 2-093, BIA 2-194, BIA 2-195 and Oxcarabazepine Glucuronide Plasma Concentrations

All glucoronides were higher in the renal impaired group compared to the healthy group. No evaluable statistical data for plasma BIA 2-093 glucuronide were available for Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1; and Group 5 / Group 1
Results of the statistical analysis for BIA 2-194 glucuronide and BIA 2-195 glucuronide and oxcarbazepine glucuronide for the various groups are given below:

Table: Statistical Analysis for BIA 2-194 Glucuronide Pharmacokinetic Variables (Group 5 / Group 1)

Variable	Normal renal function group (n = 8)		ESRD		%Ratio (Impaired/Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean		
C_{max} (ng/mL)	8	1859.856	8	5492.564	295.32	(174.39 ; 500.11)
AUC(0-12h) (hr·ng/mL)	8	7331.567	8	35785.113	488.10	(247.99 ; 960.69)
AUC(0-t_{last})	8	30908.430	8	35785.113	115.78	(70.90 ; 189.06)
AUC(0-∞) (hr·ng/mL)	7	32721.848	3	70803.857	216.38	(119.61 ; 391.44)
$t_{½.z}$ (hr)	7	14.587	3	6.158	42.22	(22.90 ; 77.83)
CL/F (l/hr)	7	24.448	3	11.299	46.21	(25.55 ; 83.61)
V_z/F (L)	7	514.508	3	100.372	19.51	(9.93 ; 38.31)
CL_R *(mL/h)*	7	5978.205	2	222.460	3.72	(1.52 ; 9.13
T_{max} (hr)♠	8	3.500	8	9.000	p-value: 0.2142	

Table: Statistical Analysis for BIA 2-195 Glucuronide Pharmacokinetic Variables (Group5 / Group 1)

Variable	Normal renal function group (n = 8)		ESRD		%Ratio (Impaired/Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean		
C_{max} (ng/mL)	8	1859.856	8	5492.564	295.32	(174.39 ; 500.11)
AUC(0-12h) (hr·ng/mL)	8	7331.567	8	35785.113	488.10	(247.99 ; 960.69)
AUC(0-t_{last})	8	30908.430	8	35785.113	115.78	(70.90 ; 189.06)
AUC(0-∞) (hr·ng/mL)	7	32721.848	3	70803.857	216.38	(119.61 ; 391.44)
$t_{½,z}$ (hr)	7	14.587	3	6.158	42.22	(22.90 ; 77.83)
Cl/F (l/hr)	7	24.448	3	11.299	46.21	(25.55 ; 83.61)
V_z/F (L)	7	514.508	3	100.372	19.51	(9.93 ; 38.31)
CL_R (mL/h)	2	11818.700		204.491	1.73	(0.30 ; 9.94)
T_{max} (hr)♠	8	10.500	8	9.000	p-value: 7487	

No Statistical analysis could be done for oxcarbazepine glucuroninde in the ESRD group.

Table: Statistical Analysis for BIA 2-194 Glucuronide Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

Variable (unit)	Normal renal function group		Mild renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean			n	LSMean			n	LSMean		
C_{max} (ng/mL)	8	1859.856	8	965.910	51.93	(30.67 ; 87.95)	8	3345.884	179.90	(106.23 ; 304.65)	88	3307.121	177.82	(105.00 ; 301.12
AUC(0-12h) (hr·ng/mL)	8	7331.567	8	3423.590	46.70	(23.17 ; 94.12)	8	20172.971	275.15	(139.80 ; 541.57)	8	13770.050	187.82	(95.42 ; 369.67)
AUC(0-t_{last}) (hr·ng/mL)	8	30908.430	8	29229.005	94.57	(57.91 ; 154.43)	8	151800.613	491.13	(300.75 ; 802.01)	8	214696.690	694.62	(425.37 ; 1134.31)
AUC(0-∞) (hr·ng/mL)	7	32721.848	5	43424.699	132.71	(80.25 ; 219.46)	8	191192.927	584.30	(374.59 ; 911.42)	7	379148.767	1158.70	(732.08 ; 1833.95)
$t_{½z}$ (hr)	7	14.587	5	15.361	105.30	(62.67 ; 176.95)	8	36.687	251.50	(158.97 ; 397.91)	7	64.718	443.67	(276.24 ; 712.58)
CL/F (l/hr)	7	24.448	5	18.423	75.35	(45.57 ; 124.62)	8	4.184	17.11	(10.97 ; 26.70)	7	2.110	8.63	(5.45 ; 13.66)
V_z/F (L)	7	514.508	5	408.256	79.35	(44.75 ; 140.69)	8	221.464	43.04	(25.95 ; 71.41)	7	197.008	38.29	(22.70 ; 64.59)
CL_R *(mL/h)*	7	5978.205	5	5060.970	84.66	(43.94 ; 163.09)	8	1215.017	20.32	(11.38 ; 36.28)	8	471.232	7.88	(4.33 ; 14.34)
T_{max} (hr)♣	8	3.500	8	6.500	p-value: 0.3297		8	7.875	p-value: 0.1867		8	48.000	p-value: 0.0085	

Table: Statistical Analysis for BIA 2-195 Glucuronide Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

Variable (unit)	Normal renal function group		Mild renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean			n	LSMean			n	LSMean		
C_{max} (ng/mL)	8	45.423	8	70.154	154.45	(90.95 ; 262.27)	8	128.289	282.43	(166.32 ; 479.60)	8	241.309	531.25	(312.85 ; 902.12)
AUC(0-12h) (hr·ng/mL)	8	124.987	8	175.080	140.08	(63.67 ; 308.20)	8	186.959	149.58	(67.99 ; 329.11)	8	266.151	212.94	(.78 ; 468.52)
AUC(0-t_{last}) (hr·ng/mL)	8	722.113	8	1909.525	264.44	(152.67 ; 458.03)	8	7914.180	1095.98	(632.75 ; 1898.33)	8	15199.287	2104.84	(1215.20 ; 3645.77)
AUC(0-∞) (hr·ng/mL)	2	652.003	5	4076.488	625.23	(169.45 ; 2306.85)	5	13440.478	2061.41	(558.70 ; 7605.86)	2	67493.638	10351.73	(2174.40 ; 49281.92)
$t_{½,z}$ (hr)	2	9.673	5	38.004	392.90	(103.11 ; 1497.16)	5	55.807	576.95	(151.41 ; 2198.52)	2	143.611	1484.70	(300.07 ; 7346.05)
CL/F (l/hr)	2	1226.988	5	196.247	15.99	(4.33 ; 59.01)	5	59.522	4.85	(1.31 ; 7.90)	2	11.853	0.97	(0.20 ; 4.60)
V_z/F (L)	2	17122.746	5	10759.804	62.84	(30.14 ; 131.01)	5	4792.246	27.99	(13.42 ; 58.35	2	2455.769	14.34	(5.96 ; 34.51)
CL_R (mL/h)	2	11818.700	5	2127.533	18.00	(5.45 ; 59.43)	5	648.431	5.49	(1.66 ; 18.11)	2	111.116	0.94	(0.23 ; 3.92)
T_{max} (hr)♠	8	10.500	8	10.500	p-value: 0.6007		8	48.000	p-value: 0.0060		8	60.000	p-value: 0.0044	

♠ Medians, p-value according to Wilcoxon signed rank test

Table: Statistical Analysis for Oxcarbazepine Glucuronide Pharmacokinetic Variables (Group 2 / Group 1; Group 3 / Group 1; Group 4 / Group 1)

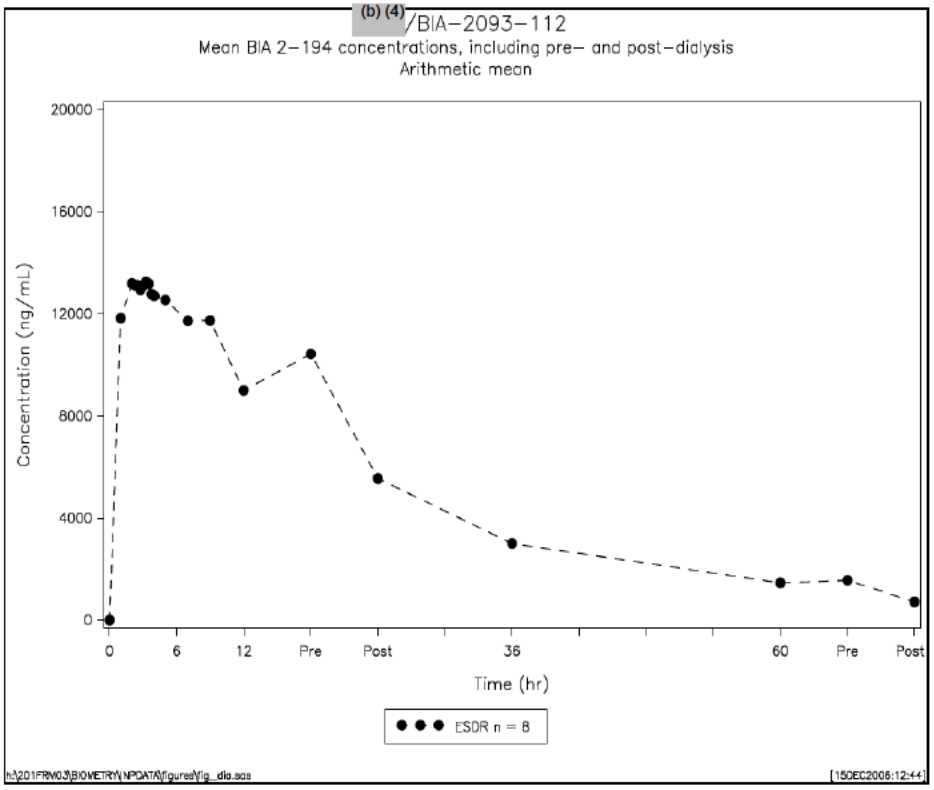
Variable (unit)	Normal renal function group		Mild renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Moderate renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio	Severe renal impairment group		%Ratio (Impaired/ Control	95% Confidence Interval of ratio
	n	LSMean	n	LSMean			n	LSMean			n	LSMean		
C_{max} (ng/mL)	8	73.344	8	127.355	173.64	(111.47 ; 270.50)	8	274.301	373.99	(240.08 ; 582.61)	8	617.056	841.32	(540.07 ; 1310.61)
AUC(0-12h) (hr·ng/mL)	8	459.448	8	1014.619	220.83	(143.09 ; 340.82)	8	1788.980	389.38	(252.30 ; 600.93)	8	2956.018	643.38	(416.89 ; 992.94)
AUC(0-t_{last}) (hr·ng/mL)	8	921.249	8	3436.694	373.05	(224.08 ; 621.04)	8	14892.883	1616.60	(971.06 ; 2691.26)	8	42677.397	4632.56	(2782.70 ; 7712.15)
AUC(0-∞) (hr·ng/mL)	6	1781.225	8	6045.430	339.40	(149.54 ; 770.31)	8	18699.650	1049.82	(462.55 ; 2382.73)	6	47844.264	2686.03	(1118.34 ; 6451.31)
$t_{½,z}$ (hr)	6	14.907	8	25.105	168.41	(81.21 ; 349.26)	8	31.456	211.01	(101.75 ; 437.61)	6	34.958	234.51	(107.53 ; 511.46)
CL/F (l/hr)	6	449.129	8	132.331	29.46	(12.98 ; 66.87)	8	42.782	9.53	(4.20 ; 21.62)	6	16.721	3.72	(1.55 ; 8.94)
V_z/F (L)	6	9659.169	8	4792.861	49.62	(32.85 ; 74.95)	8	1941.452	20.10	(13.31 ; 30.36)	6	843.303	8.73	(5.62 ; 13.57)
CL_R (mL/h)	6	7238.548	8	2810.965	38.83	(19.88 ; 75.85)	6	1033.801	14.28	(7.31 ; 27.90)	6	351.552	4.86	(2.37 ; 9.94)
T_{max} (hr)♠	8	9.000	8	9.000	p-value: 0.3450		8	24.000	p-value: 0.0750		8	36.000	p-value: 0.0125	

♠ Medians, p-value according to Wilcoxon signed rank test

- AUC (tlast) and AUC(0-∞): these values increased markedly with increasing renal impairment of all glucuronides.

BIA 2-194 Dialysate and Filter Plasma Concentrations

The following figure presents the mean plasma BIA 2-194 concentrations including pre- and post-dialysis:



ESRD Patients:

The ESRD group was mostly not comparable to the other groups since they were dialyzed 12 – 18 hours after medication, which complicated comparisons.
The mean plasma concentrations of BIA 2-195, oxcarbazepine, BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide for the ESRD group markedly exceed those of the groups with less impairment. The mean plasma concentrations of these metabolites were effectively reduced by dialysis. However, it was only after the second dialysis that plasma concentrations were reduced to low levels approaching LLOQ. In the case of BIA 2-194 glucuronide, BIA 2-195 glucuronide and oxcarbazepine glucuronide plasma concentrations increased markedly after the first dialysis. The reason for these increases is not clear.

Urine Concentrations:

BIA 2-093 Urine Concentrations

Mean BIA 2-093 urine concentrations were higher in the subjects in the normal renal function group than in the mild, moderate and severe renal impairment groups.

BIA 2-194 Urine Concentrations

Major metabolites recovered in urine were BIA 2-194 and BIA 2-194 glucuronide, the sum of which corresponded to approximately 90% of all metabolites recovered in urine. However, the fraction of BIA 2-194 decreased and the fraction of BIA 2-194 glucuronide increased with the degree of the renal impairment: in the control group, BIA 2-194 corresponded to approximately 52% and BIA 2-94 glucuronide to 41% of total renal excretion; the mild renal impairment group showed similar results (49% versus 44%), but a marked change was found in the moderate and renal impairment groups (29% versus 61% and 22% versus 66%, respectively).

BIA 2-195 and Oxcarbazepine Urine Concentrations

Pharmacokinetics of the minor metabolites in plasma and urine (BIA 2-195, BIA 2-195 glucuronide, oxcarbazepine and oxcarbazepine glucuronide) also showed to be significantly affected by renal impairment. Systemic exposure to all those metabolites showed to increase with the degree of the renal impairment, as consequence of longer half-lives and lower total body clearance and renal clearance. These findings all point to a reduced ability of kidneys with impaired function to excrete BIA 2-093 or its metabolites. The magnitude of this reduction depends on the degree of renal impairment.

Dose Adjustment in Renal Impaired subjects:

Based on the results of the study dosing adjustment is necessary in patients with renal impairment.

Sponsors Proposed Dosing Adjustment: Sponsor's proposal is given in the following Table:

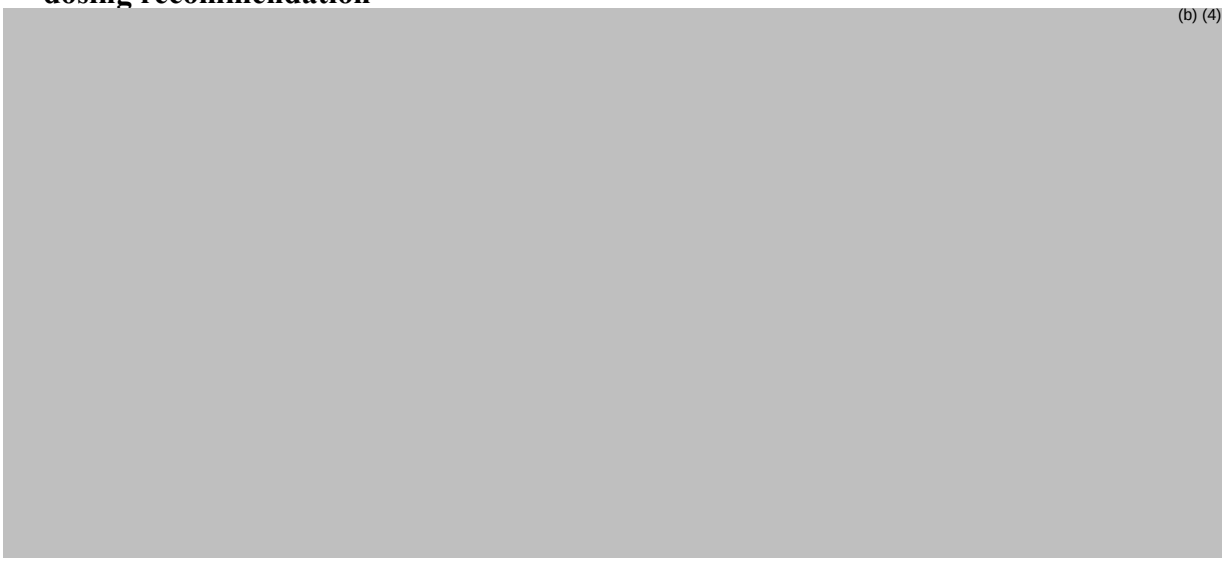
(b) (4)

Simulations were conducted to predict the plasma concentration time profiles based on sponsor proposed dosing recommendations for the titration phase. The proposal of (b) (4)

The plasma concentration profile for eslictabazepine in the renally impaired based on sponsor's dosing recommendation is given in the following Figure:

Figure: Plasma concentration profile in the renally impaired based on sponsor's dosing recommendation

(b) (4)

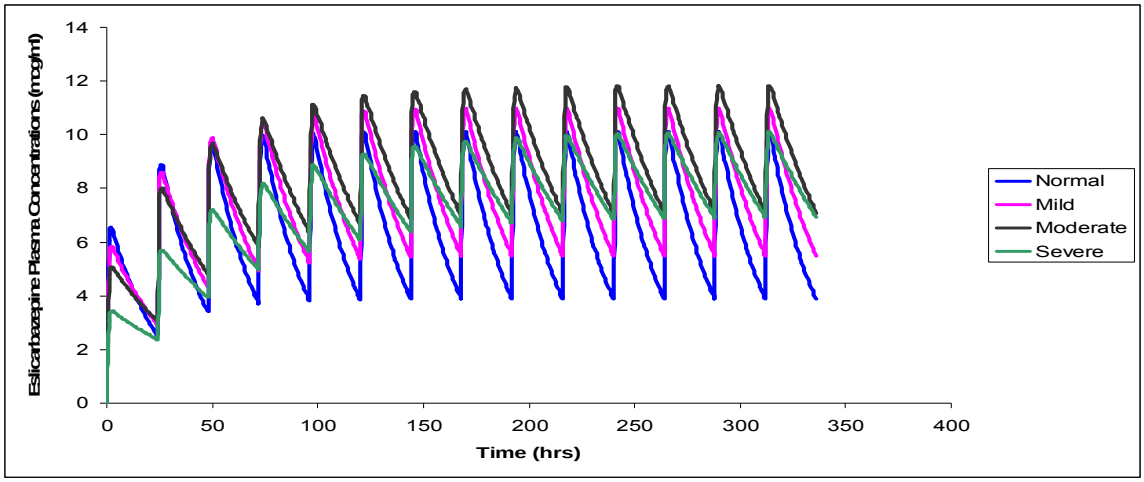


Reviewer Proposed Dosing Adjustment:

Initial Dose (Titration Phase):
Simulations were conducted to allow everyday dosing in the titration phase. The reviewer propose dosing for the titration phase is given in the following Table:

	Normal	Mild	Moderate	Severe
Initial Dosing Recommendations	400 mg QD	350 mg QD or 400 mg QD	300 mg QD	200 mg QD

The simulated plasma concentration profile based on these recommendations is shown in the following figure. These simulations propose once daily administration during the titration phase.



The predicted Cmax and Cmin in patients with various degrees of renal impaired based on the proposed dose is given in the following Table. As shown the Cmax and Cmins are similar in all categories.

	Normal	Mild	Moderate	Severe
Initial Dosing Recommendations	400 mg QD	350 mg QD or 400 mg QD	300 mg QD	200 mg QD
Cmax (µg/ml)	10.17	11.08	11.8	10.10
Cmin (µg/ml)	3.992	5.56	7.14	6.99

The limitation of this dosing recommendation is the unavailability of lower strengths (200, 300 and 350 mg). Although the (b) (4) 800 mg tablets are scored on one side. Given this it may be acceptable to dose the mild impiarement patients with 400 mg QD initially instead of 350 mg.

Maintenance Dose:

(b) (4) The reviewer recommends that the maximum recommended dose in the moderate and severe renal patients be 600 mg because if these patients are given the 1200 mg dose their exposure with be significantly higher than the healthy subjects.
Simulations were conducted to demonstrate the higher exposure in the renal impaired (moderate and severe) if given a 1200 mg dose.

Figure: Plasma concentration profile at steady state at the sponsor and reviewer recommended doses

The sponsor was requested to clarify their recommendation. In theie response of Nov 16th 2009, they recommended capping at 600 mg too.

The predicted steady sate Cmax and AUC after a 600 mg dose in given in the following Table, which supports the use of this dose.

Table: Steady-State PK Parameters in Renal Impairment Subjects (Simulation) and In Epileptic Patients (Observed data from PK Sub-Study)

	Epileptic Patients	**Moderate**	**Severe**
	1200 mg QD	**600 mg QD**	**600 mg QD**
Mean C_{max} (ng/mL) (Range)	22957 (12770, 32753)	19323	24250
Mean $AUC_{0\text{-}tau}$ (ng*h/mL) (Range)	336147 (214866, 539385)	352125	465070

Therefore the final dosing recommendations are given in the following Table:

Dosing Recommendations	Normal	Mild	Moderate	Severe
Initial	400 mg QD for 1 week	400 mg QD for 1 week	300 mg QD for 1 week	200 mg QD for 1 week
Maximum	1200 mg QD	1200 mg QD	600 mg QD	600 mg QD

Overall Conclusions:

- Systemic exposure to all those metabolites showed to increase with the magnitude of the renal impairment, as consequence of longer half-lives and lower total body clearance and renal clearance.
- Dialysis was effective in removing the drug and its metabolites from the circulation of patients with end-stage renal disease.
- Dose Adjustments are recommended as given above in the moderate and severe impaired patients.

IN VITRO STUDIES

IN VITRO DRUG INTERACTIONS:

1. Study 524: In vitro Binding of [^{14}C]-ESL to Plasma Proteins and Blood Cells

The *in vitro* plasma protein and blood cell binding of [^{14}C]-SEP-0002093 was assessed in rat, dog, and man. Plasma protein binding was measured by ultrafiltration performed on pooled plasma samples from each species. Blood cell partitioning was measured, using centrifugation, on pooled blood samples from male rats, dogs, and humans, and the proportion of [^{14}C]-SEP-0002093 in blood associated with red blood cells was calculated.

Plasma protein binding of [^{14}C]-SEP-0002093 was low in samples from the rat and dog over the concentration range of 0.05-2 µg/mL, with mean values of 28.2% (range 26.6% to 30.6%) and 40.5% (range 38.4% to 42.0%), respectively. Higher plasma protein binding was observed in man compared to the rat or dog, with a mean value of 60.7% (range 58.2% to 63.1%) across the concentration range of 0.05-2 µg/mL. No evidence of concentration-dependent binding was observed in any species.

Mean blood/plasma concentration ratios for [^{14}C]-SEP-0002093 in rat, dog, and human blood were 0.840 (range 0.799-0.884), 0.826 (range 0.746-0.888), and 0.751 (range 0.700-0.800), respectively. The mean percentages of [^{14}C]-SEP-0002093 associated with red blood cells in rat, dog, and human blood were 33.4% (range 29.0% to 37.6%), 36.9% (range 28.3% to 45.3%), and 37.8% (range 24.0% to 47.0%), respectively. Overall, association of [^{14}C]-SEP-0002093 with red blood cells was moderate, and independent of concentration in all three species.

In conclusion, plasma protein binding of [^{14}C]-SEP-0002093 in man was higher than seen in the rat or the dog, but was still moderately low, with no evidence of concentration-dependent binding. The blood cell binding of [^{14}C]-SEP-0002093 was moderate in all species with no evidence of concentration-dependent binding.

2. Study 525: Determination of the *In Vitro* Plasma Protein Binding and Blood Cell Binding of [^{14}C]-BIA 2-194 in Rat and Man

The *in vitro* plasma protein and blood cell binding of [^{14}C]-eslicarbazepine was assessed in rat and man.

Plasma protein binding was measured by ultrafiltration performed on pooled plasma samples from each species. Blood cell partitioning was measured, using centrifugation, on pooled blood samples from male rats and humans, and the proportion of [^{14}C]-eslicarbazepine in blood associated with red blood cells was calculated.

Over the concentration range of 1-100 µg/mL, the mean plasma protein binding of [^{14}C]-eslicarbazepine was 25.4% (range 24.8% to 26.4%) in rat and 30.1% (26.3% to 33.3%) in man. This concentration range extends well above the mean (SD) C_{max} of 22.96

(5.26) µg/mL observed in adult epileptics receiving SEP-0002093 1200 mg QD maintenance therapy (PK Sub-study, 2093-301). There was no significant evidence of inter-species differences or concentration-dependence. The mean blood cell binding of [^{14}C]-eslicarbazepine was 43.1% (range 38.0% to 46.1%) in rat and 46.2% (43.2% to 51.1%) in man. Again, no significant inter-species differences or concentration-dependent binding was observed.

In conclusion, plasma protein binding of [^{14}C]-eslicarbazepine was low and blood cell binding of [^{14}C]-eslicarbazepine was moderate in rat and man over the examined concentration range of 1-100 µg/mL. There was no evidence of species differences or concentration dependent binding observed.

Reviewer's Comment: The protein binding observed in this study over a wider concentration range was lower than that observed in Study 525. One difference noted was that the total protein content in this study was determined to be 55g/L, which is below the normal range for human plasma (57g/L) where as the protein content in Study 524 was 59g/L. Nevertheless, the protein binding is low and as such drug interactions related to protein binding are unlikely.

3. **Study 529: Displacement of plasma protein binding by other drugs for BIA 2-194**

The mean values of binding of BIA 2-194, warfarin, diazepam, digoxin, phenytoin and tolbutamide to plasma proteins were 37.2%, 97.5%, 97.2%, 32.6%, 85.9% and 97.3%, respectively.

The mean values of binding of [14C] BIA 2-194 to plasma proteins in the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide following ultrafiltration were 31.3%,28.9%,36.6%,28.0% and 25.5%, respectively. Therefore the binding of [14C] BIA 2-194 to plasma proteins was not affected by the presence of any of the other compounds studied.
The mean values of binding of [14C] warfarin, [14C] diazepam, [3H] digoxin, [14C] phenytoin and [14C] tolbutamide to plasma proteins in the presence of BIA 2-194 following ultrafiltration were 96.6%,96.6%,36.3%,83.1% and 96.4%, respectively.

Conclusion: The binding of [14C] BIA 2-194 to plasma proteins was unaffected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide and the binding of [14C] warfarin, [14C] diazepam, [3H] digoxin, [14C] phenytoin and [14C] tolbutamide was unaffected by the presence of BIA 2-194. Therefore no plasma protein binding displacement was observed.

4. **Study 533: To assess induction potential of BIA 2-194**

The study was performed *in vitro* with freshly isolated human hepatocytes from 3 donors using selective probe substrates to determine the CYP activities. For comparison, the effects of known inducers of these CYP isoforms were assessed in parallel incubations.

Treatment of hepatocytes with increasing concentrations of BIA 2-194 (10 µg/mL to 100 µg/mL) had little effect (ie < 2 fold) on the metabolism of [14C]-7-ethoxycoumarin (used as a CYP1A probe) or on the conversion of [14C]-testosterone to its 6β-OH metabolite (CYP3A4 probe). The CYP2C19 mediated conversion of [14C]-*S*-mephenytoin to the 4-OH metabolite could only be assessed in a single donor at the end of the exposure period, however, in this individual no induction was observed. In contrast, archetypal inducers of CYP isoforms were shown to induce the relevant routes of metabolism in the hepatocytes. 3-methylcholanthrene, omeprazole were used as positive controls for CYP1A2, Rifampin for CYP2C19 and rifampin and dexamethasone for CYP3A4.

Table: Formation of Total [14C]-7-Ethoxycoumarin Metabolites Following Incubation with Human Hepatocytes Treated with BIA 2-194, Known CYP Inducers or Dose Vehicle

Treatment	Total Metabolite Formation								
	Donor A			Donor B			Donor C		
	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction
Media Control	*	*	N/A	4923	1231	N/A	6550	1637	N/A
DMSO Control	*	*	N/A	10999	2750	N/A	8307	2077	N/A
BIA 2-194 (10 µg/mL)	1721	430.4	0.44	12071	3018	1.10	8964	2241	1.08
BIA 2-194 (50 µg/mL)	1793	448.2	0.46	13744	3436	1.25	9957	2489	1.20
BIA 2-194 (100 µg/mL)	2081	520.2	0.54	13201	3300	1.20	11007	2752	1.33
Omeprazole (30 µM)	7919	1980	2.04	20580	5145	1.91	12649	3162	1.23
3-MC (2 µM)	10290	2573	2.65	36100	9025	3.35	20770	5193	2.02
Rifampicin (3 µM)	3778	944.6	0.97	18778	4694	1.74	16099	4025	1.57
Dexamethasone (10 µM)	3328	832.1	0.86	11869	2967	1.10	10135	2534	0.99
Phenytoin (300 µM)	2683	670.9	0.69	14326	3581	1.33	11514	2878	1.12
DMSO control	3878	969.6	N/A	10778	2695	N/A	10264	2566	N/A
Ethanol control	1369	342.3	N/A	4526	1132	N/A	8085	2021	N/A

Reviewer's Comment: It appears that assessment of induction potential for CYP1A2 is not adequate as the positive controls do not show the same magnitude of induction of CYP1A2 as expected, 14-24 fold for omeprazole and 6-26 fold for 2-MC, although the inducer concentrations were adequate in the test system.

Table: Formation of 6β-OH Testosterone Following Incubation of [14C]-Testosterone with Human Hepatocytes Treated with BIA 2-194, Known CYP Inducers or Dose Vehicle

Treatment	6β-OH Testosterone Formation								
	Donor A			Donor B			Donor C		
	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction	Mean pmol/10^6 cells	Mean pmol/10^6 cells/h	Fold induction
Media Control	764.3	191.1	N/A	1575	393.8	N/A	596.4	149.1	N/A
DMSO Control	3421	855.4	N/A	3839	959.8	N/A	1154	288.4	N/A
BIA 2-194 (10 µg/mL)	3361	840.2	0.98	3289	822.3	0.86	1232	308.0	1.07
BIA 2-194 (50 µg/mL)	4436	1109	1.30	4000	1000	1.04	1354	338.4	1.17
BIA 2-194 (100 µg/mL)	5011	1253	1.46	4514	1129	1.18	1593	398.2	1.38
Omeprazole (30 µM)	1543	385.7	0.36	0	0	0	839.3	209.8	1.19
3-MC (2 µM)	550.0	137.5	0.13	1195	298.7	0.54	700.0	175.0	0.60
Rifampicin (3 µM)	18575	4644	4.33	16875	4218.8	7.70	6261	1565.2	5.41
Dexamethasone (10 µM)	5507	1377	1.29	4982	1246	2.27	1261	315.2	1.09
Phenytoin (300 µM)	4261	1065	0.99	13239	3310	6.04	3379	844.6	2.92
DMSO control	4286	1071	N/A	2193	548.2	N/A	1157	289.3	N/A
Ethanol control	560.7	140.2	N/A	1161	290.2	N/A	703.6	175.9	N/A

Reviewer's Comment: Inducer concentration for Rifampin (10 µM) and dexamethasone (33-250 µM) is lower than recommended. The positive controls did not show sufficient level of induction with dexamethazone either, probably due to lower concentrations of inducer used.

The induction of Phase II enzymes is shown in the following Table:

Phase II Metabolism in Fresh Human Hepatocytes		
	Fold Induction	
	Glucuronidation	**Sulphation**
10 µg/mL eslicarbazepine	1.03±0.07	0.67±0.34
50 µg/mL eslicarbazepine	1.07±0.12	0.90±0.27
100 µg/mL eslicarbazepine	1.04±0.12	0.89±0.45
Omeprazole (CYP1A)	1.79±0.23	1.17±0.28
3-MC (CYP1A)	2.20±0.32	1.56±0.19
Rifampicin (CYP3A)	1.60±0.15	1.04±0.26

Values presented as mean ±SD of 3 experiments.

Conclusion:
BIA 2-194 is not considered to be an inducer of CYP3A4 and Phase II enzymes in human hepatocytes *in vitro*. The induction of CYP1A2, has not been adequately evaluated.

5. Study 534: To assess induction potential of BIA 2-194, BIA 2-195 and oxcarbazepine for CYP3A4

This study was designed to assess the potential of BIA 2-194, BIA 2-195 or Oxcarbazepine to induce hepatic drug metabolizing enzymes. The study was performed *in vitro* by incubating freshly isolated human hepatocytes from 3 donors, for 72 h, with increasing concentrations of BIA 2-194, BIA 2-195 or Oxcarbazepine. The metabolic competence and potential induction of the test system was established in parallel using probe substrates as markers of specific inducible enzymes.
Treatment of hepatocytes from all three donors with increasing concentrations of BIA 2-194 (1 µg/mL to 30 µg/mL), BIA 2-195 (0.3 µg/mL to 10 µg/mL) or oxcarbazepine (0.1 µg/mL to 3 µg/mL) showed no dose dependant effect on the metabolism of [14C]-testosterone to 6β-OH testosterone, indicative of CYP3A4 activity, or androstenedione. In contrast, the archetypal inducer of CYP3A4, rifampicin was shown to induce the relevant routes of metabolism in the hepatocytes.

Table: Formation of 6β-OH Testosterone Following Incubation of [14C]-Testosterone with Human Hepatocytes Treated with BIA 2-194, Rifampicin or Dose Vehicles

Treatment	6β-OH Testosterone Formation								
	Donor I			Donor II			Donor III		
	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #
Media Control	187 180 172	180 ± 7.52	-	224 248 *	236 ± 16.6	-	554 318 412	428 ± 119	-
Vehicle Control (MeCN:dH_2O, 1:1, v/v)	187 148 151	162 ± 21.7	-	503 371 315	396 ± 96.4	-	465 592 632	563 ± 87.5	-
BIA 2-194 (1 µg/mL)	226 179 164	190 ± 32.4	1.17 (13.7%)	* 270 352	311 ± 58.1	-	535 603 668	602 ± 66.6	1.07 (21.7%)
BIA 2-194 (3 µg/mL)	242 208 244	231 ± 20.0	1.43 (16.7%)	348 233 549	377 ± 160	-	642 487 741	623 ± 128	1.11 (22.5%)
BIA 2-194 (10 µg/mL)	217 213 177	202 ± 22.1	1.25 (14.6%)	312 411 411	378 ± 57.4	-	456 549 677	560 ± 111	1.00 (20.3%)
BIA 2-194 (30 µg/mL	212 231 206	216 ± 12.9	1.34 (15.7%)	328 419 453	400 ± 64.5	1.01 (11.9%)	794 738 865	799 ± 63.8	1.42 (28.8%)
Rifampicin Vehicle Control (DMSO)	207 158 168	178 ± 25.6	-	1002 874 1045	974 ± 88.7	-	1485 1323 1486	1431 ± 93.9	-
Rifampicin (3 µM)	1614 1875 1066	1518 ± 413	8.55	8954 8468 7406	8276 ± 792	8.50	7858 7291 6016	7055 ± 943	4.93

Fold induction when compared to vehicle control. Values in parenthesis are percentage of fold induction relative to positive control inducer, rifampicin.
- No fold induction.

Table: Formation of 6βOH Testosterone Following Incubation of [14C]-Testosterone with Human Hepatocytes Treated with BIA 2-195, Rifampicin or Dose Vehicles

Treatment	6β-OH Testosterone Formation								
	Donor I			Donor II			Donor III		
	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #
Media Control	168 183 183	178 ± 8.70	-	346 346 245	312 ± 58.5	-	903 645 681	743 ± 140	-
Vehicle Control (MeCN)	183 181 162	175 ± 11.6	-	406 319 396	374 ± 47.6	-	521 613 581	571 ± 46.6	-
BIA 2-195 (0.3 µg/mL)	181 150 142	158 ± 20.4	-	253 428 367	350 ± 88.5	-	367 443 520	443 ± 76.2	-
BIA 2-195 (1 µg/mL)	204 168 156	183 ± 24.2	1.04 (12.2%)	369 513 448	443 ± 72.1	1.19 (14.0%)	569 539 500	536 ± 34.6	-
BIA 2-195 (3 µg/mL)	202 246 192	213 ± 28.9	1.22 (14.3%)	670 407 309	462 ± 187	1.24 (14.6%)	621 539 907	689 ± 194	1.21 (24.5%)
BIA 2-195 (10 µg/mL)	130 190 194	171 ± 35.8	-	411 613 531	518 ± 101	1.39 (16.4%)	733 872 391	665 ± 248	1.16 (23.5%)
Rifampicin Vehicle Control (DMSO)	207 158 168	178 ± 25.6	-	1002 874 1045	974 ± 88.7	-	1485 1323 1486	1431 ± 93.9	-
Rifampicin (3 µM)	1614 1875 1066	1518 ± 413	8.55	8954 8468 7406	8276 ± 792	8.50	7858 7291 6016	7055 ± 943	4.93

Fold induction when compared to vehicle control. Values in parenthesis are percentage of fold induction relative to positive control inducer, rifampicin.
- No fold induction.

Table: Formation of 6β-OH Testosterone Following Incubation of [14C]-Testosterone with Human Hepatocytes Treated with Oxcarbazepine, Rifampicin or Dose Vehicles

Treatment	6β-OH Testosterone Formation								
	Donor I			Donor II			Donor III		
	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #	pmol/10^6 cells/h	Mean pmol/10^6 cells/h ± SD	Fold Induction #
Media Control	137 134 127	133 ± 5.29	-	352 195 373	307 ± 97.3	-	340 650 451	480 ± 157	-
Vehicle Control (DMSO)	219 271 186	225.14 ± 42.7	-	1220 891 1048	1053 ± 164	-	882 1219 1213	1105 ± 193	-
Oxcarbazepine (0.1 µg/mL)	225 187 189	200 ± 21.2	-	1064 1097 1142	1101 ± 39.1	1.05 (12.4%)	779 1100 1343	1074 ± 283	-
Oxcarbazepine (0.3 µg/mL)	184 149 178	170 ± 18.7	-	463 774 921	719 ± 234	-	537 845 1131	838 ± 297	-
Oxcarbazepine (1 µg/mL)	157 163 199	173 ± 22.7	-	1176 1110 1190	1158 ± 42.7	1.10 (12.9%)	1083 1541 1320	1315 ± 229	1.19 (24.1%)
Oxcarbazepine (3 µg/mL)	164 161 169	165 ± 4.01	-	914 1037 1223	1058 ± 155	1.00 (11.8%)	1279 1183 1308	1256 ± 65.6	1.14 (23.1%)
Rifampicin Vehicle Control (DMSO)	207 158 168	178 ± 25.6	-	1002 874 1045	974 ± 88.7	-	1485 1323 1486	1431 ± 93.9	-
Rifampicin (3 µM)	1614 1875 1066	1518 ± 413	8.55	8954 8468 7406	8276 ± 792	8.50	7858 7291 6016	7055 ± 943	4.93

Fold induction when compared to vehicle control. Values in parenthesis are percentage of fold induction relative to positive control inducer, rifampicin.
- No fold induction.

The archetypal inducer of CYP3A4, rifampicin, was shown to induce the relevant routes of metabolism in the hepatocytes by approximately 5- to 8-fold compared to 1.0- to 1.43-fold for eslicarbazepine.

Conclusion: BIA 2-194, BIA 2-195 or Oxcarbazepine are not considered to be inducers of CYP3A4 in human hepatocytes *in vitro*.

6. Study 530: To assess the potential of BIA 2-194 to inhibit Human hepatic enzyme system

Incubations performed with probe substrate in the presence of CYP isozyme selective inhibitors (single concentration) were used as positive controls. The following inhibitors were used: furafylline (CYP1A2; 10 μM), 8-methoxysporalen (CYP2A6; 6 μM), sulphaphenazole (CYP2C9; 10 μM), tranylcypromine (CYP2C19; 20 μM), quinidine (CYP2D6; 0.5 μM), diethyldithiocarbamate (CYP2E1; 10 μM), ketoconazole (CYP3A4, 0.5 μM) and cyclohexene oxide (EH, 100 μM). However, for some reactions (CYP2B6, CYP4A9/11, UGT1A1 and UGT1A6) there are no commercially available potent selective inhibitors.

The effect of increasing concentrations of eslicarbazepine (10-100 μg/mL) on the rate of probe substrate metabolism was determined. This concentration range extends above the mean (SD) Cmax of 22.96 (5.26) μg/mL observed in adult epileptics receiving SEP-0002093 1200 mg QD maintenance therapy

The effect of BIA 2-194 on the activity of individual CYP isoforms is described in Tables 1 and 2 as mean values. These data are presented as both reaction rates and as %of control activities.

Table: Effects of Eslicarbazepine on Human Hepatic Microsomal Enzyme Activity

Eslicarbazepine (µg/mL)						
Enzyme	**10**	**50**	**100**	**100 (pre-inc)**	**Inhibitor Test**	
CYP 1A2	95.9	95.6	85.6	106.8	33.4	Furafylline (10 µM)
CYP 2A6	91.5	100.1	91.6	92.0	17.0	8-Methoxysporalen (6 µM)
CYP 2B6	94.6	103.6	105.9	106.5	-	NA
CYP 2C9	89.8	81.2	62.5	77.5	7.0	Sulphaphenazole (10 µM)
CYP 2C19	113.1	110.0	101.9	83.7	8.9	Tranylcipromine (20 µM)
CYP 2D6	120.8	117.2	115.1	87.7	49.1	Quinidine (5 µM)
CYP 2E1	101.6	86.8	92.4	75.5	45.7	Diethylthiocarbamate (10 µM)
CYP 3A4 (Tst)	108.8	105.6	105.7	102.6	31.7	Ketoconazole (0.5 µM)
CYP 3A4 (Nif)	77.5	78.9	73.4	100.0	54.8	Ketoconazole (0.5 µM)
CYP 3A4 (Mdz)	124.3	125.5	79. 9	75.0	11.7	Ketoconazole (0.5 µM)
CYP 4A9/11	93.6	90.7	93.2	128.7	-	NA
UGT1A1	115.5	186.8	138.8	119.4	-	NA
UGT1A6	91.13	106.6	108.9	116.8	-	NA
EH	99.35	137.4	124.1	117.2	37.5	Cyclohexene oxide (100 µM)

NA – Not Available; Results are expressed as % of control activity.
pre-inc - pre-incubation; Tst – Testosterone; Nif – Nifedipine; Mdz - Midazolam

- There was a moderate inhibition of CYP2C9 mediated tolbutamide 4-hydroxylation. At the top concentration (100 µM) the rate of tolbutamide 4-hydoxlyation was decreased by *ca* 38%, and pre-incubation decreased formation by *ca* 23 %. Sulphaphenazole, a probe inhibitor of CYP2C9, inhibited metabolite formation by *ca* 93 % at a concentration of 10 µM.
- Co-incubation of midazolam with BIA 2-194 at concentrations up to 100 µM produced mild inhibition of midazolam 1'-hydroxylase activity *(ca* 20 %). Pre-incubation with BIA 2-194 also decreased the reaction rate by ca 25 %. Ketoconazole, a probe inhibitor of CYP3A4 decreased midazolam 1'-hydroxylation by ca 88 % at a concentration of 0.5 µM. Co-incubation of nifedipine with BIA 2-194 at concentrations up to 100 µM appeared to cause a slight decrease in nifedipine oxidation (to a maximum of ca 27%), whereas pre-incubation of nifedipine with the test item had no effect on the reaction rate. Ketoconazole, a probe inhibitor of CYP3A4 decreased nifedipine oxidation by ca 45 % at a concentration of 0.5 µM.
- There was a mild activation of UGT1A1 mediated ethinylestradiol glucuronidation.

Conclusions:

In vitro studies with human liver microsomes have demonstrated that BIA 2-194 has little inhibitory effect on drug metabolizing enzymes that mediate the metabolism of therapeutic agents. It only showed moderate inhibition of CYP2C9. It can therefore, be

considered unlikely that BIA 2-194 would inhibit the CYP-dependent, UGTdependent or epoxide hydrolase metabolism of any co-administered drugs at concentrations that are likely to be achieved *in vivo.* Ki or IC50 values were not reported in this study, although inhibition appears to be low when compared to the positive controls. The inhibition potential for CYP2C8 has not been evaluated.

7. Study 531: An In Vitro Study to Examine the Effect of BIA 2-194, BIA 2-195 and Oxcarbazepine on Human Hepatic CYP2C19 Enzyme Activity

Co-incubation at concentrations up to 30 µg/mL or pre-incubation with BIA 2-194 had no significant inhibitory effect on the rate of metabolite formation (Table 1). Tranylcypromine, a selective inhibitor of CYP2C19, decreased activity by ca 75 % at a concentration of 20 µM.

Table 1 ***The Effect of Increasing Concentrations of BIA 2-194 on CYP2C19-Mediated S-Mephenytoin 4-Hydroxylation***

[BIA 2-194] (µg/mL)	pmoles/min/mg formed	Mean pmol/min/mg	% Control	Mean % Control
Control	46.86	44.68	104.88	100.00
	42.04		94.09	
	45.14		101.03	
1	38.94	42.27	87.15	94.60
	43.42		97.17	
	44.45		99.49	
3	34.80	41.01	77.89	91.77
	45.14		101.03	
	43.07		96.40	
10	43.07	40.66	96.40	91.00
	35.15		78.66	
	43.76		97.94	
30	39.28	38.13	87.92	85.35
	35.84		80.21	
	39.28		87.92	
Tranylcypromine Control	8.27	8.96	92.31	100.00
	8.96		100.00	
	9.65		107.69	
Tranylcypromine	0.00	2.18	0.00	24.36
	3.10		34.62	
	3.45		38.46	
15 min Pre-Inc Control	48.35	52.24	92.55	100.00
	51.69		98.94	
	56.69		108.51	
15 min Pre-Inc BIA 2-194	41.68	45.02	79.79	86.17
	36.68		70.21	
	56.69		108.51	
30 min Pre-Inc Control	45.02	55.58	81.00	100.00
	63.36		114.00	
	58.36		105.00	
30 min Pre-Inc BIA 2-194	51.69	55.02	93.00	99.00
	51.69		93.00	
	61.69		111.00	

Co-incubation with increasing concentrations of BIA 2-195 (up to 10 µg/mL) resulted in a minor inhibition of CYP2C19 activity, the maximum inhibition being ca 25 % at 10 µg/*mL*. BIA 2-195 had no inhibitory effect on the rate of metabolite formation following 15 min pre-incubation, but a ca 12 % inhibition was observed following 30 min pre-incubation. (Table 2)

Table 2 ***The Effect of Increasing Concentrations of BIA 2-195 on CYP2C19-Mediated S-Mephenytoin 4-Hydroxylation***

[BIA 2-195] (µg/mL)	pmoles/min/mg formed	Mean pmol/min/mg	% Control	Mean % Control
Control	43.42	42.96	101.07	100.00
	40.66		94.65	
	44.80		104.28	
0.3	51.34	47.90	119.52	111.50
	45.49		105.88	
	46.86		109.09	
1	52.03	41.12	121.12	95.72
	42.38		98.66	
	28.95		67.38	
3	30.67	33.54	71.39	78.07
	42.04		97.86	
	27.91		64.97	
10	31.36	32.28	72.99	75.13
	34.46		80.21	
	31.01		72.19	
Tranylcypromine Control	8.27	8.96	92.31	100.00
	8.96		100.00	
	9.65		107.69	
Tranylcypromine	0.00	2.18	0.00	24.36
	3.10		34.62	
	3.45		38.46	
15 min Pre-Inc Control	58.36	65.03	89.74	100.00
	75.03		115.38	
	61.69		94.87	
15 min Pre-Inc BIA 2-195	70.03	65.58	107.69	100.85
	68.36		105.13	
	58.36		89.74	
30 min Pre-Inc Control	56.69	53.36	106.25	100.00
	46.69		87.50	
	56.69		106.25	
30 min Pre-Inc BIA 2-195	65.03	47.24	121.88	88.54
	55.02		103.13	
	21.68		40.63	

Co-incubation with oxcarbazepine resulted in a moderate inhibitory effect upon CYP2C19, the greatest effect being a ca 30 % inhibition at ca 1 or 3 µg/mL. Pre-incubation with oxcarbazepine had no inhibitory effect on the rate of metabolite formation (Table 3).

Table 3 ***The Effect of Increasing Concentrations of Oxcarbazepine on CYP2C19-Mediated S-Mephenytoin 4-Hydroxylation***

[Oxcarbazepine] (µg/mL)	pmoles/min/mg formed	Mean pmol/min/mg	% Control	Mean % Control
Control	11.03	11.83	93.20	100.00
	12.75		107.77	
	11.72		99.03	
0.1	12.41	10.91	104.85	92.23
	11.72		99.03	
	8.61		72.82	
0.3	13.09	11.83	110.68	100.00
	11.37		96.12	
	11.03		93.20	
1	6.55	7.70	55.34	65.05
	8.96		75.73	
	7.58		64.08	
3	5.86	8.50	49.51	71.84
	12.06		101.94	
	7.58		64.08	
Tranylcypromine Control	8.27	8.96	92.31	100.00
	8.96		100.00	
	9.65		107.69	
Tranylcypromine	0.00	2.18	0.00	24.36
	3.10		34.62	
	3.45		38.46	
15 min Pre-Inc Control	36.68	30.57	120.00	100.00
	33.35		109.09	
	21.68		70.91	
15 min Pre-Inc Oxcarbazepine	35.01	33.35	114.55	109.09
	38.35		125.45	
	26.68		87.27	
30 min Pre-Inc Control	25.01	32.79	76.27	100.00
	35.01		106.78	
	38.35		116.95	
30 min Pre-Inc Oxcarbazepine	35.01	38.90	106.78	118.64
	40.02		122.03	
	41.68		127.12	

Conclusions:

A low level of inhibition was observed as the concentrations of BIA-194, BIA 195 and oxcarbazepine were increased. Based upon this *in vitro* study, clinically relevant

inhibition of CYP2C19 by BIA 2-194, BIA 2-195 and oxcarbazepine would be considered unlikely.

8 . Study 532: An In Vitro Study to Examine the Effect of BIA 2-194, BIA 2-195 and Oxcarbazepine on Human Hepatic CYP2C19 Enzyme Activity

A low level of inhibition was observed over the concentration range examined **in study 531.** In this study, the effect of a wider concentration range of BIA 2-194, BIA 2-195 and Oxcarbazepine on the rate of S-mephenytoin metabolite formation was examined, which is likely to span the therapeutic range of each drug.

Co-incubation with increasing concentrations of BIA 2-194 resulted in inhibition of ca 20 %, *ca* 30 % and *ca* 50 % at 30, 100 and 300 ug/mL, respectively. An IC50 value, the concentration of BIA 2-194 producing 50 % inhibition of metabolism, of *ca* 232 ug/mL was calculated. (Table 1 and 2)

Table 1 ***The Effect of Increasing Concentrations of BIA 2-194 on CYP2C19 Mediated S-Mephenytoin 4-Hydroxylation***

[BIA 2-194] (μg/mL)	pmols/min/mg Formed	pmols/min/mg Mean +/- SD	% Control	% Control Mean +/- SD
Control	23.12	22.91	100.90	100.00
	21.10		92.10	
	24.52	1.72	107.00	
0.1	20.26	23.32	88.44	101.76
	21.47		93.68	
	28.22	4.29	123.16	18.72
1	21.03	21.20	91.78	92.50
	22.00		96.00	
	20.56	0.73	89.73	3.20
3	22.28	22.31	97.24	97.39
	22.08		96.34	
	22.59	0.26	98.57	1.12
10	21.33	22.82	93.09	99.58
	23.72		103.51	
	23.40	1.30	102.14	5.66
30	17.60	18.37	76.83	80.19
	19.97		87.16	
	17.54	1.39	76.56	6.05
100	12.30	15.91	53.69	69.42
	19.42		84.76	
	16.00	3.56	69.82	15.54
300	10.32	11.57	45.05	50.49
	14.85		64.83	
	9.53	2.87	41.58	12.54
Tranylcypromine Control	6.29	7.18	87.56	100.00
	8.69		120.99	
	6.57	1.31	91.45	
Tranylcypromine	3.97	3.79	55.28	52.72
	3.91		54.41	
	3.48	0.27	48.46	3.71
15 min Pre-inc Control	24.60	23.88	103.02	100.00
	18.50		77.48	
	28.54	5.05	119.50	
15 min Pre-Inc BIA 2-194	31.90	28.39	133.60	118.87
	27.92		116.94	
	25.33	3.31	106.08	13.86
30 min Pre-Inc Control	28.24	23.27	121.37	100.00
	25.22		108.40	
	16.34	6.19	70.23	
30 min Pre-Inc BIA 2-194	27.55	26.41	118.38	113.51
	28.96		124.46	
	22.73	3.26	97.70	14.03

Table 2 ***The Effect of Increasing Concentrations of BIA 2-194 on CYP2C19 Mediated S-Mephenytoin 4-Hydroxylation (DMSO as solvent)***

[BIA 2-194] (μg/mL)	pmols/min/mg Formed	pmols/min/mg Mean +/- SD	% Control	% Control Mean +/- SD
Control	19.47	16.91	115.1	100
	15.42		91.19	
	15.84	2.23	93.67	
0.1	15.61	16.30	92.35	96.41
	15.57		92.10	
	17.71	1.22	104.8	7.24
1	17.16*			
	3.86*			
	3.37*			
3	14.72	15.22	87.05	90.03
	16.94		100.2	
	14.00	1.53	82.83	9.07
10	16.29	14.88	96.35	88.04
	17.56		103.9	
	10.80	3.59	63.91	21.23
30	17.46	13.66	103.3	80.81
	10.91		64.54	
	12.62	3.40	74.63	20.08
100	10.50	11.33	62.11	67.02
	12.15		71.89	
	11.34	0.83	67.07	4.89
300	8.57	6.72	50.72	39.74
	5.74		33.93	
	5.84	1.61	34.56	9.51
Tranylcypromine Control	21.19	20.36	104.0	100
	19.93		97.84	
	19.98	0.71	98.11	
Tranylcypromine	11.63	11.20	57.09	54.98
	13.59		66.74	
	8.37	2.64	41.10	12.95
15 min Pre-Inc Control	48.08	46.84	102.6	100
	42.34		90.40	
	50.10	4.02	107.0	
15 min Pre-Inc BIA 2-195	54.72	41.11	116.8	87.77
	35.32		75.40	
	33.29	11.83	71.08	25.26
30 min Pre-Inc Control	46.32	41.38	111.9	100
	44.37		107.2	
	33.44	6.94	80.83	
30 min Pre-Inc BIA 2-195	44.36	43.64	107.2	105.5
	45.67		110.4	
	40.88	2.48	98.79	5.99

*data from this sample rejected

Activity in the absence of DMSO and BIA 2-194 was 44.18 ± 3.01 pmol/min/mg

Co-incubation with increasing concentrations of BIA 2-195 resulted in inhibition of CYP2C19 activity of *ca* 21 % at 100 ug/mL and *ca* 50 % at 300 ug/ml. (Table 3)

Table 3 ***The Effect of Increasing Concentrations of BIA 2-195 on CYP2C19 Mediated S-Mephenytoin 4-Hydroxylation***

[BIA 2-195] (µg/mL)	pmols/min/mg Formed	pmols/min/mg Mean +/- SD	% Control	% Control Mean +/- SD
Control	9.13	8.90	102.57	100.00
	9.77		109.83	
	7.80	1.01	87.60	
0.1	8.52	6.76	95.76	75.97
	7.03		79.02	
	4.73	1.91	53.12	21.48
1	7.03	6.54	78.97	73.48
	7.50		84.33	
	5.08	1.28	57.14	14.40
3	11.86	9.23	133.28	103.75
	7.86		88.37	
	7.97	2.28	89.61	25.58
10	8.44	8.42	94.89	94.68
	8.68		97.49	
	8.16	0.26	91.65	2.93
30	10.96	9.84	123.22	110.61
	10.26		115.34	
	8.30	1.38	93.28	15.52
100	6.33	7.00	71.14	78.68
	7.01		78.76	
	7.67	0.67	86.15	7.51
300	4.48	4.49	50.31	50.49
	3.93		44.17	
	5.07	0.57	57.00	6.42
Tranylcypromine Control	6.29	7.18	87.56	100.00
	8.69		120.99	
	6.57	1.31	91.45	
Tranylcypromine	3.97	3.79	55.28	52.72
	3.91		54.41	
	3.48	0.27	48.46	3.71
15 min Pre-Inc Control	21.76	21.31	102.12	100.00
	18.85		88.44	
	23.32	2.27	109.44	10.66
15 min Pre-Inc BIA 2-195	28.56	27.52	134.04	129.15
	20.82		97.72	
	33.18	6.24	155.71	29.30
30 min Pre-Inc Control	18.93	25.95	72.93	100.00
	29.84		114.98	
	29.09	6.10	112.09	
30 min Pre-Inc BIA 2-195	18.61	22.31	71.69	85.98
	21.67		83.49	
	26.67	4.07	102.75	15.68

The results at the 10 µg/ml, are not the same as seen in the previous study, (25% inhibition vs.5% seen in this study)

Co-incubation with increasing concentrations of Oxcarbazepine resulted in inhibition of CYP2C19 activity of *ca* 28 % at 100 ug/mL and *ca* 74 % at 300 ug/ml. An IC50 of 168 ug/mL was calculated. (Table 4)

Table 4 ***The Effect of Increasing Concentrations of Oxcarbazepine on CYP2C19 Mediated S-Mephenytoin 4-Hydroxylation***

[Oxcarbazepine] (μg/mL)	pmols/min/mg Formed	pmols/min/mg Mean +/- SD	% Control	% Control Activity Mean +/- SD
Control	6.81	7.90	86.22	100.00
	8.40		106.30	
	8.49	0.94	107.49	
0.1	11.48	8.86	145.35	112.16
	6.65		84.22	
	8.44	2.44	106.91	30.90
1	9.05	10.22	114.61	129.41
	10.89		137.90	
	10.72	1.02	135.73	12.87
3	9.67	9.31	122.38	117.88
	11.00		139.30	
	7.26	1.90	91.95	23.99
10	8.95	8.22	113.28	104.12
	5.90		74.64	
	9.83	2.06	124.44	26.13
30	7.94	7.57	100.48	95.81
	8.12		102.84	
	6.64	0.81	84.11	10.20
100	6.07	5.67	76.83	71.84
	4.54		57.50	
	6.41	1.00	81.19	12.61
300	2.23	2.06	28.29	26.06
	2.81		35.59	
	1.13	0.85	14.31	10.81
Tranylcypromine Control	6.29	7.18	87.56	100.00
	8.69		120.99	
	6.57	1.31	91.45	
Tranylcypromine	3.97	3.79	55.28	52.72
	3.91		54.41	
	3.48	0.27	48.46	3.71
15 min Pre-Inc Control	26.01	25.04	103.87	100.00
	25.35		101.23	
	23.76	1.15	94.90	4.61
15 min Pre-Inc Oxcarbazepine	23.92	25.56	95.53	102.06
	24.02		95.90	
	28.74	2.75	114.75	10.99
30 min Pre-Inc Control	21.49	22.79	94.31	100.00
	16.38		71.88	
	30.49	7.14	133.81	
30 min Pre-Inc Oxcarbazepine	21.88	24.40	96.03	107.08
	27.93		122.58	
	23.38	3.15	102.62	13.82

Conclusions:

BIA 2-194, BIA 2-195 and Oxcarbazepine produced moderate to major inhibition of CYP2C19 metabolism at the higher concentrations investigated in this study. The concentrations required to produce inhibition may be considered to be at the upper. end of those attained in clinical use. Calculated IC50 values for eslicarbazepine and oxcarbazepine were well above the clinically relevant range at 232 and 168 µg/mL, respectively, and inhibition by (R)-licarbazepine of approximately 50% at 300 µg/mL. The Cmax of BIA 2-194 at the highest dose is 22.96, I/Ki will be 0.196
Clinically significant inhibition of the metabolism of co-administered CYP2C19 substrates is possible, although at the borderline.

Pre incubation of BIA 2-194, BIA 2-195 and Oxcarbazepine, in the presence of microsomal protein and co-factor, had no significant inhibitory effect on the rate of metabolite formation suggesting that CYP2C19 mediated metabolism is not mechanism-based.

Reviewer's Comment:

Study 530 did not show inhibition of CYP2C19, but showed moderate inhibition of CYP2C9. The sponsor conducted two studies to evaluate CYP2C19 inhibition by BIA 2-194, BIA 2-195 and oxcarbazepine, as Trilpetal is an inhibitor of CYP2C19. The results show some inhibition at higher substrate concentration. A 30% inhibition of CYP2C19 by BIA 2-194 was not observed in Study 530.

9. Study 528: Investigation of the potential inhibitory effect of a range of anti-epileptic drugs on the metabolism of [14C] BIA 2-093

[14C] BIA 2-093 (30 ug/ml) was incubated in human liver microsomes (1 mg/ml) for 1, 5 and 10 minutes, and also incubated in the presence of anti-epileptic drugs (acetazolamide, clobazam, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and sodium valproate; incubated at 2 x human plasma Cmax) or drug vehicle alone, for 10 minutes only. The metabolism of [14C] BIA 2-093 was measured by HPLC using on-line radiochemical detection. The percentage formation of each metabolite was determined from the fractional conversion of [14C] BIA 2-093 apparent from the radiochromatograms.

A single metabolite, the S (+) enantiomer of BIA 2-005 (BIA 2-194) was present in all incubation samples. Following 10 minutes incubation in the absence of anti-epileptic drugs, only *ca* 7 % parent BIA 2-093 remained. Inhibition of BIA 2-093 metabolism by anti-epileptic drugs was found to be no greater than *ca* 5 % of vehicle control values.

Table: Mean formation of metabolites following incubation of [14C] BIA 2-093 in the presence of anti-epileptic drugs in human liver microsomes

Sample/Antiepileptic Drug	Percentage Formation of Eslicarbazepine
Control	96.5 ± 1.29, 90.7 ± 2.40[a]
Vehicle control	95.1 ± 0.216, 89.3 ± 2.34[a]
Acetazolamide (60 µg/mL)	94.4 ± 1.52
Clobazam (2 µg/mL)	92.1 ± 1.21
Clonazepam (0.2 µg/mL)	93.6 ± 0.972
Gabapentin (20 µg/mL)	90.1 ± 0.207
Lamotrigine (20 µg/mL)	90.2 ± 0.688
Phenobarbital (100 µg/mL)	97.5 ± 3.53
Phenytoin (60 µg/mL)	90.0 ± 2.55
Primidone (40 µg/mL)	95.8 ± 0.728
Sodium valproate (400 µg/mL)	92.8 ± 0.102

Conclusions:

Based on the findings of this *in vitro* study, no clinically significant drug interactions may be predicted, with regard to the inhibition of metabolism of BIA 2-093 by anti-epileptic drugs.

DRUG-DRUG INTERACTION STUDIES

Study 125: Effects of eslicarbazepine acetate on the pharmacokinetics of Metformin in healthy volunteers

ESL metabolites are excreted in urine in the unchanged form or conjugated with glucuronic acid and their clearance showed to be dependent on renal function. Metformin is a commonly used antidiabetic; its elimination occurs mainly via kidney and is affected by renal function. Therefore, an interaction study between ESL and metformin at the renal excretion level could be hypothesized. This study aimed to investigate whether multiple-dose administration of ESL affects the pharmacokinetics of metformin.

Objectives:

- To investigate whether multiple-dose administration of eslicarbazepine acetate (ESL, BIA 2-093) affects the pharmacokinetics of metformin.
- To investigate the tolerability of concomitant administration of ESL and metformin.

The study design is as follows:

<table>
<tr><td>Study Design</td><td>This was a single-centre, open-label, randomised, two-way crossover study in healthy young male and female volunteers. The study consisted of 2 consecutive treatment periods separated by a washout period of 14 days or more.</td></tr>
<tr><td>Study Population</td><td>N= 20 Healthy subjects, 19 completed, one dropped due to personal reasons
Gender: 10 M and 10F
Age: 27 (24-32)
Weight: 72 (18-104) lbs</td></tr>
<tr><td>Treatment Group</td><td>Two treatment periods with 14 Day washout
<table><tr><th rowspan="2">Treatment sequence</th><th colspan="2">Treatment Periods</th></tr><tr><th>1</th><th>2</th></tr><tr><td>A</td><td>Eslicarbazepine acetate plus Metformin</td><td>Metformin</td></tr><tr><td>B</td><td>Metformin</td><td>Eslicarbazepine acetate plus Metformin</td></tr></table>
1200 mg MD ESL Day 1-6, 850 mg SD Metformin on Day 5</td></tr>
<tr><td>Dosage and Administration</td><td>In accordance with the metformin hydrochloride dosing recommendations, Risidon® should be administered with a meal. Thus, it was administered with the morning meal. On Day 5 of the ESL plus Metformin period, ESL was administered concomitantly with the Risidon® (i.e., with the morning meal). On the other days, ESL was administered without regard to meals.

Products were administered orally, in the morning with approximately 240 mL of water.</td></tr>
</table>

	Eslicarbazepine acetate tablets (batch number 050059-L Risidon® 850 mg (batch number 110096
Sampling: Blood	<u>For BIA 2-005:</u> Predose on Days 1, 3, 4, 5 and 6 <u>Metformin:</u> Predose, and ½, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-metformin dose on Day 5 Metformin mean elimination half-life ($t_{1/2}$) is approximately 6.5 h; thus, a 48-h plasma concentration versus time profiling appears to be adequate because it corresponds to more than 5 elimination half-lives. Metformin mean t_{max} occurs at 2.25 h post-dose; therefore, blood sampling time-points were schedule to be more frequent during the first 6 hours after dosing.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation <u>Plasma</u> BIA 2-005 10 ng/ml Meformin 50 ng/ml Method: HPLC/MS method Linear Range: 10 – 10000 ng/mL for BIA 2-005. 50-4500 ng/ml for metformin <u>BIA 2-005:</u> Quality control concentrations: 30, 1200, 7500 ng/ml Inter-day precision: % CV: < 3.1 Inter-day accuracy: 96.5-103.3%. <u>Metformin:</u> Quality control concentrations: 25, 1500, 3000 ng/ml Inter-day precision: % CV: < 15% Inter-day accuracy: % deviation -1.86-5.96
PK Assessment	AUC0-12, AUC0-24, AUC0-∞,Cmax, Tmax, t1/2, Cl/F. V/F Since metformin is usually administered in a twice-daily regimen, AUC_{0-12} was also considered a primary study variable for the assessment of the effect of ESL on the metformin pharmacokinetic parameters, together with $AUC_{0-\infty}$ and C_{max}.
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

<u>Pharmacokinetic Results:</u>

<u>BIA 2-005:</u>

Plasma levels of BIA 2-005 were assayed at pre-dose (Cmin) on Days 1, 3, 4, 5 and 6, to demonstrate that the steady-state of plasma concentrations has been achieved

Mean results are presented in the following Table:

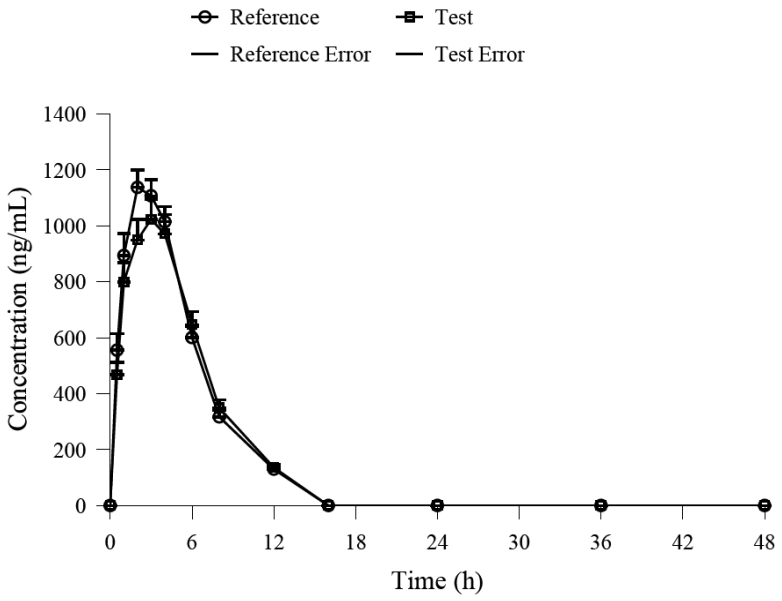
Table: Mean (CV%) Cmin of BIA 2-005 at Days 1, 3, 4, 5 and 6 following oral administration of ESL 1200 mg once-daily (n=19)

	Day 1	Day 3	Day 4	Day 5	Day 6
BIA 2-005 (ng/mL)	0	9841 (11.8)	10851 (19.6)	11117 (15.7)	11196 (17.7)

Metformin:

Metformin plasma concentration-time profiles following administration of metformin with ESL (Test) and metformin alone (Reference) are displayed in the following Figure.

Figure: Metformin plasma concentration-time profile (mean±SEM) following an oral metformin 850 mg single-dose administered alone or concomitantly with the 5th dose of ESL 1200 mg administered once-daily for 6 days.



Arithmetic mean (coefficient of variation, %) pharmacokinetic parameters of metformin following an oral 850 mg single-dose administered alone or concomitantly with the 5th dose of once-daily ESL 1200 mg for 6 days were as follows:

Table; Mean pharrmacokinetic parameters of metformin following a single oral dose of 850 mg administered with and without ESL

Pharmacokinetic parameter	Metformin	
	Metformin with ESL	Metformin alone
C_{max} (ng/mL)	1091 (27.6)	1224 (21.9)
t_{max} (h)	2.66 (46.9)	2.53 (40.4)
AUC_{0-12} (ng.h/mL)	6864 (27.0)	7160 (21.8)
$AUC_{0-\infty}$ (ng.h/mL)	7362 (26.7)	7688 (21.4)
λ_z (h^{-1})	0.272 (11.4)	0.255 (10.3)
$t_{1/2}$ (h)	2.58 (13.3)	2.74 (10.0)
CL/F (L/h)	126480 (35.7)	116018 (22.9)
V/F (L)	476016 (44.4)	459343 (25.3)

The geometric mean ratios are given in the following Table:

Table: 90%CI of *Test/Reference* GMR for metformin Cmax, AUC0-12 and AUC0-∞ following oral administration of a metformin 850 mg single-dose alone (*Reference*) and concomitantly with the 5th dose of ESL 1200 mg once-daily for 6 days (*Test*)

Metformin PK parameters		*Test/Reference*
C_{max}	GMR (%)	0.88
	90% CI	0.77; 1.00
AUC_{0-12}	GMR (%)	0.95
	90% CI	0.85; 1.06
$AUC_{0-\infty}$	GMR (%)	0.95
	90% CI	0.86; 1.05

GMR – Geometric mean ratio; 90% CI – 90% confidence intervals

The extent of exposure to metformin, as reflected by AUC0-12 and AUC0-∞, is within the pre-specified bioequivalence acceptance interval (0.80, 1.25). Formal bioequivalence could not be demonstrated for metformin Cmax because the 90% CI of the GMR is not fully contained within the acceptance interval. The differences in pharmacokinetic parameters between the two treatment periods are mainly due to one subject (#017) who presented markedly lower values following administration of metformin with ESL than following administration of metformin alone. Such difference may to be due to an acute gastroenteritis reported by this subject on the metformin plus ESL period.
No tmax statistical significant difference was found between *Test* and *Reference* (p=0.120).

Conclusions:
Once-daily administration of ESL 1200 mg had no relevant effect on the systemic exposure to metformin pharmacokinetics in healthy subjects and on the basis of the results of this study no adjustment in the dose of metformin appears to be necessary when it is co-administered with ESL.

Study 126: Effects of eslicarbazepine acetate on the pharmacokinetics of Gliclazide in healthy volunteers

This study does not allow a definite conclusion regarding the possible effect of ESL on the pharmacokinetics of gliclazide because the formulation of gliclazide used showed to have poor and erratic bioavailability in both treatment periods. The gliclazide formulation used in this study was Diamicron® 80 mg tablets, batch number 74208, expiry date 04/2010, manufactured on 13APR2007 by [redacted] (b) (4) and marketed by Servier Portugal - Especialidades Farmacêuticas, Lda, Av. António Augusto de Aguiar. Poor bioavailability with a gliclazide formulation marketed by Les Laboratoires Servier Poland has been reported in the literature.

Study 107: The effect of BIA 2-093 on the steady-state pharmacokinetics of digoxin in healthy volunteers

Objectives

Primary: To investigate the effects of multiple-dose administration of BIA 2-093 on the steady-state pharmacokinetics of digoxin in healthy subjects.
Secondary: To investigate the tolerability and safety of co-administration of BIA 2-093 and digoxin.

The study design is as follows:

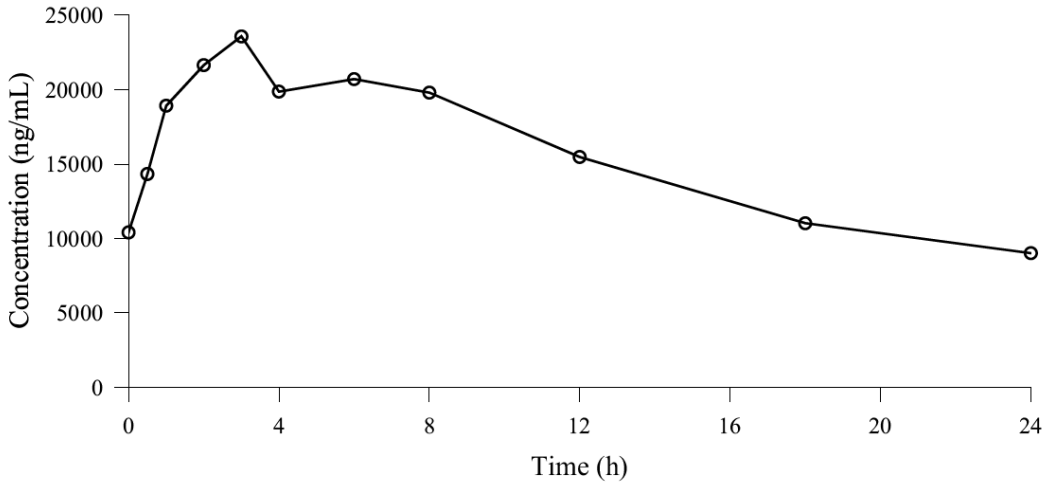
Study Design	Single centre, multiple-dose, double-blind, randomized, placebo-controlled, two-way crossover study. The study consisted of two 8-day treatment periods separated by a washout of 10 or more days. During each of the treatment periods the volunteers received either a daily oral dose of BIA 2-093 1200 mg once-daily (od) or matching placebo, concomitantly with a dose of digoxin (days 1 and 2: loading dose of 0.5 mg/day; days 3 to 8: 0.25 mg/day).
Study Population	Number of subjects planned = 12 subjects (6 male and 6 female) Number of subjects analyzed = 13 subjects (6 male and 7 female). Age: Healthy volunteers aged between 18 and 45 years. Gender: male and female. Weight: 53 to 102 kg Race: 12 Caucasians, 1 black
Treatment Group	Either (A) a daily oral dose of BIA 2-093 1200 mg once-daily (od) plus digoxin or (B) matching placebo plus digoxin.
Dosage and Administration	Two 8-day periods in which subjects were administered BIA 2-093 1200 mg once-daily orally in one period and placebo in the other period, concomitantly with digoxin (days 1 and 2: loading dose of 0.5 mg/day; days 3 to 8: 0.25 mg/day). The 1200 mg dose of BIA 2-093 consisted of 2 tablets strength 600 mg (batch number 20168). The Placebo dose consisted of 2 tablets matching BIA 2-093 600 mg tablets (batch number 20014L). Digoxin (Lanoxin™, GlaxoWellcome, Portugal) tablets strength 0.25 mg (batch number 1N165). Diet: Overnight fast for at least 8 hours Washout: The study consisted of two 8-day treatment periods separated by a washout period of 10 days or more.
Sampling	Blood sampling for digoxin assay: on days 6 and 7 predose; day 8, pre-dose, 1/2 , 1, 2, 3, 4, 6, 8, 8, 12, 18 and 24 h post-dose. Blood sampling for BIA-2005 assay: Days 6 and 7: pre-dose; day 8:

	pre-dose, 1/2, 1, 2, 3, 4, 6, 8, 12, 18 and 24 h pose-dose.
Analysis	BIA-2-093: below LOQ of the assay BIA 2-005 (active metabolite): LC/MS/MS LOQ: 10 ng/mL Digoxin RIA with sensitivity 0.1 ng/mL LOQ: 19.5 – 5000 pg/mL and range of measurements of 249 – 4002 pg/mL Quality control samples Intra-assay precision (%CV): 5.2 – 11.1% Inter-assay precision (%CV): 5.2- 12.0% Accuracy: 92.5% to 115.4%
PK Assessment	Non-compartmental methods Cmax, Tmax, Cmin, Tmin, AUCτ, t ½ , PTF (Peak to trough fluctuation) = 100*((Cmax – Cmin)/Cav)
Safety Assessment	Number, severity and relation to treatment of the adverse events reported; heart rate and blood pressure; 12-lead electrocardiogram; and clinical laboratory safety tests (haematology, plasma biochemistry, coagulation and urinalysis).
PD Assessment	None

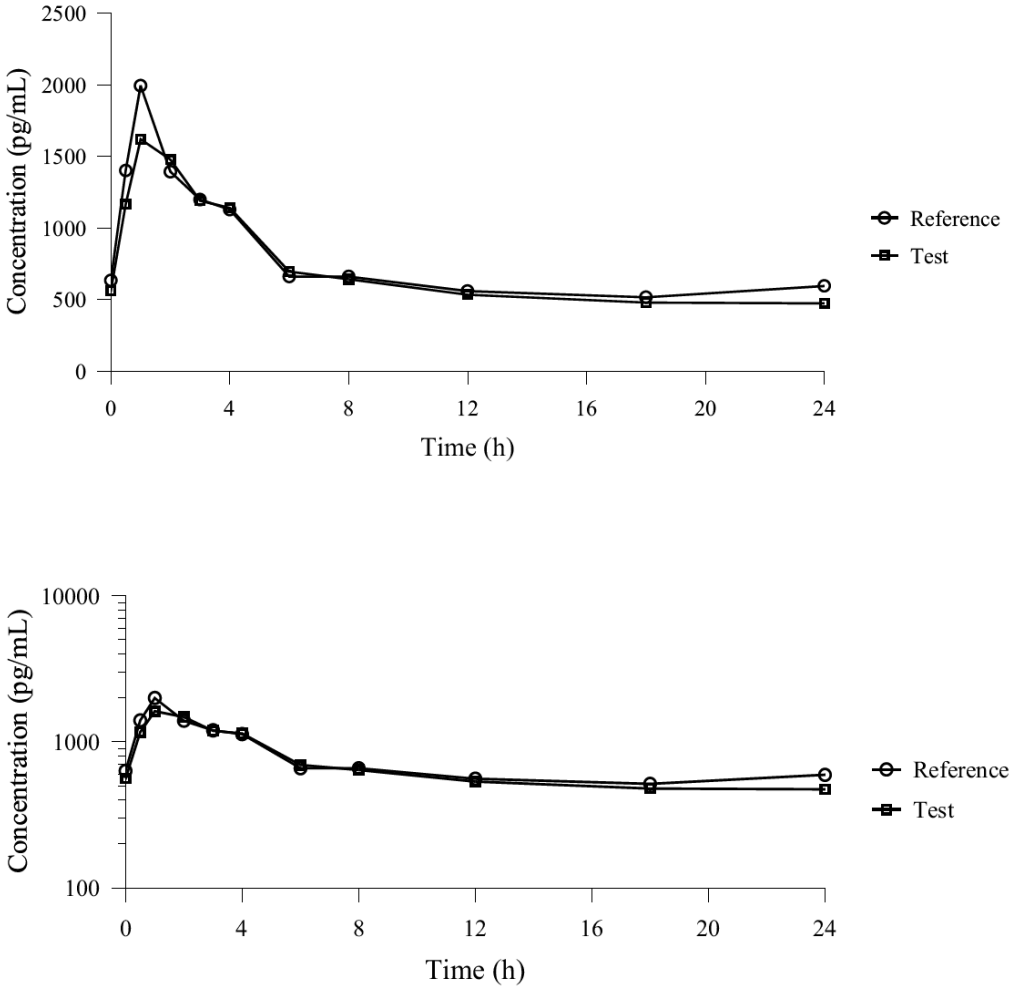
Pharmacokinetic Results

Mean concentration-time profiles for BIA 2-005 and Digoxin are presented in the following figures.

Mean plasma BIA 2-005 concentration-time profile following the last dose of an 8-day oral regimen of Digoxin and BIA 2-093 1200 mg once-daily treatment (n=12)



Mean steady-state serum digoxin concentration-time profiles following oral administration with BIA 2-093 (Test) and with Placebo (Reference) (n=12)



Plasma levels of BIA 2-005 were assayed at pre-dose (Cmin) on Days 6, 7 and 8, to demonstrate that the steady-state of plasma concentrations has been achieved. Mean results are in the following table.

Mean Cmin (pre-dose) of BIA 2-005 at Days 6, 7 and 8 of an 8-day oral regimen of Digoxin plus BIA 2-093 1200 mg once-daily (n=12)

	Day 6	Day 7	Day 8
BIA 2-005 (ng/mL)	9586 (1963)	8609 (2945)	10403 (3637)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.

Serum levels of digoxin were assayed at pre-dose (Cmin) on Days 6, 7 and 8, to demonstrate that the steady-state of plasma concentrations has been achieved. Results are provided in the following table.

Mean Cmin (pre-dose) of Digoxin at Days 6, 7 and 8 of an 8-day oral regimen of Digoxin plus BIA 2-093 1200 mg or Placebo once-daily (n=12)

	Serum digoxin (pg/mL)		
	Day 6	**Day 7**	**Day 8**
Digoxin + Placebo	445 (151)	452 (128)	633 (300)
Digoxin + BIA 2-093	475 (157)	522 (133)	561 (177)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.

The pharmacokinetic parameters of serum digoxin concomitantly administered with BIA 2-093 or with Placebo are summarized in the following table

Pharmacokinetic parameters of Digoxin following the last dose of an 8-day oral regimen of Digoxin and BIA 2-093 1200 mg or Placebo once-daily (n=12)

	C_{max} (pg/mL)	**t_{max}** (h)	**AUCτ** (pg.h/mL)
Digoxin + Placebo	2350 (1034)	1 (0.5-2)	17607 (5599)
Digoxin + BIA 2-093	1909 (596)	1 (0.5-4)	16595 (3801)

Results of C_{max} and AUCτ are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
t_{max} values are median with range values in parentheses.

The following table presents the point estimates and 90%CI for the comparison of Cmax and AUCt for digoxin.

Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of Cmax and AUCt of Digoxin following its concomitant administration with BIA 2-093 and Placebo

Digoxin parameters		*Test / Reference*
C_{max}	PE	0.85
	90%CI	0.68;1.07
AUCτ	PE	0.96
	90%CI	0.90;1.03

Exposure to digoxin, as reflected by the AUCt, fits the claim of bioequivalence (90% CI of 0.80 – 1.25) between Test (Digoxin plus BIA 2-093) and Reference (Digoxin plus

Placebo), with a Point Estimate (PE) of 0.96 and a 90%CI of the AUCt ratio of 0.90-1.03. However, Cmax values did not fit the claim of bioequivalence between Test and Reference, with a PE of 0.85 and a 90%CI of the Cmax ratio of 0.68-1.07. The 90%CI is not included within the 0.80-1.25 reference interval. No statistical differences were found between tmax values for Digoxin when Test and Reference were compared.

Conclusions:

BIA 2-093 1200 mg once-daily for 8-days did not affect the extent of systemic exposure to digoxin (AUCt). With respect to digoxin Cmax, BIA 2-093 significantly decreased Digoxin value by about 15% when concomitantly BIA-093 and Digoxin are concomitantly administered together. Regarding tmax, no statistical differences were found between digoxin following its concomitant administration with BIA 2-093 and Placebo. The sponsor states that since the therapeutic effect of digoxin is expected to correlate more with the extent of exposure (expressed by AUCt) than with the rate of absorption (expressed by Cmax), efficacy of Digoxin in clinical practice is not expected to be significantly affected by concomitant administration of BIA 2-093.

Safety Conclusions:

The sponsor stated that during the course of the study, 10 subjects reported a total of 22 adverse events considered possibly or definitely related to treatment. Most of the adverse events reported were mild in intensity. Adverse events considered possibly or definitely related to treatment were reported by 8 (61.5%) subjects while taking Digoxin + BIA 2-093 and by 4 (30.8%) subjects while taking Digoxin + Placebo. Two adverse events (hypertension worsened and syncope vasovagal, both classified as unrelated to treatment) were assessed as severe in intensity. The most common treatment-emergent adverse event was mental impairment, followed by somnolence, headache and tension headache.

Reviewer comments: The reviewer agrees with the sponsor's conclusions. Co-administration of Digoxin with BIA 2-093 is not expected to affect the therapeutic effect of digoxin.

Study 108: The effect of BIA 2-093 on the Steady-State Pharmacodynamic and Pharmacokinetic profiles of Warfarin in Healthy Volunteers.

Objectives: Primary: To investigate whether multiple-dose administration of BIA 2-093 has any effect on the steady-state pharmacokinetic and pharmacodynamic profiles of warfarin. Secondary: To assess the tolerability and safety of the co-administration of BIA 2-093 and warfarin.

The study design is as follows:

Study Design	Multiple-dose, open-label, single-period study consisting of three consecutive phases: - Phase A: run-in warfarin dose-finding phase (phase A), aiming to identify a warfarin daily dose that stabilizes the INR between 1.3 and 1.8; duration of this phase was to be up to 21 days. - Phase B: warfarin pharmacokinetics (PK) and international normalized ratio (INR) profiling before, during, and after a 7-day multiple-dose treatment with BIA 2-093, in which subjects were to receive 1200 mg BIA 2-093, once-daily, concomitantly with their individualized dose of warfarin defined in the run-in phase A. The aim of this phase was to assess whether BIA 2-093 affects INR and levels of warfarin when it is added to concomitant warfarin therapy. - Phase C: 7-day period in which subjects were to receive warfarin alone at their individualized doses, aiming to assess whether BIA 2-093 affects INR and trough levels of warfarin when it is removed from concomitant warfarin therapy.
Study Population	N = 12 planned (6 males and 6 females) healthy volunteers. Analyzed: 13 (7 males and 6 females) Age: 18 to 45 yrs (Mean ±SD 28.13 ± 7.25) Gender: Males and Females Weight: 67.28 ± 10.69 kg Race: Caucasians (N= 14); other (N=1)
Treatment	1200 mg dose of BIA 2-093 consisted of 2 tablets strength 600 mg (batch number 20168); oral route. Duration of treatment: Seven-day period, concomitantly with warfarin. Warfarin (Coumadin®, DuPont Pharma, USA) tablets strength 1 mg (batch number EPL451A) and 2 mg (EPO557A and EOB085A); oral route.
Dosage and Administration	Phase A: 5 mg of warfarin on Days 1 to 3 followed by a dose titration to stable pre-dosing prothrombin INR values within 1.3 to 1.8, according to frequently measured INR values. The choice of warfarin dose on any given day after Day 3 was to depend on the assessment of the INR response of the subject. Phase B: On Day 2, subjects were to start receiving an oral, once-daily dose of 1200 mg of BIA 2-093 for 7 days, in addition to the oral, once-daily individualized dose of warfarin defined in Phase A.

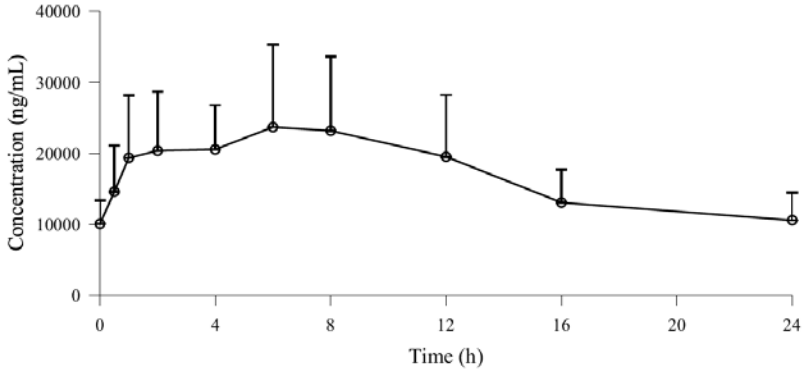
	Phase C: Warfarin alone, orally, once-daily, at their individualized doses, for 7 days. Batch number(s) for study drugs: BIA 2-093 600 mg tablets 20168 Coumadin® 1 mg tablets EPL451A Coumadin® 2 mg tablets EPO557A; EOB085A
Sampling	Phase A: Blood sampling for R- and S-warfarin assay: 3 days prior starting BIA 2-093 dosing. Phase B: On Day 1, a 24-h warfarin PK profiling was to occur: pre-dose, and ½, 1, 2, 4, 6, 8, 12,16, and 24 h post-dose. On Day 8, a 24-h warfarin PK profiling was to occur: pre-dose, and ½, 1, 2, 4, 6, 8, 12, 16, and 24 h post-dose. Trough values of R- and S-warfarin: Days 4, 6, and 7: pre-dose. Blood sampling for determination of INR: Days 1, 2, 4, 6, 7, and 8: pre-dose. Blood sampling for the BIA 2-005 assay: Day 8: pre-dose, and ½, 1, 2, 4, 6, 8, 12, 16, and 24 h post-dose; Days 2, 4, 6, and 7: pre-dose. Phase C: Blood sampling for determination of INR: Days 1, 3, 5 and 7: pre-dose; Day 8: 24 h post last-warfarin dose. Blood sampling for the R- and S-warfarin assays: Days 3, 5 and 7: pre-dose; Day 8: 24 h post last-warfarin dose. After the blood sampling on Day 8 (or premature discontinuation), subjects were to receive vitamin K until their INR values returned to pre-treatment values.
Analysis	LC/MS/MS BIA 2-093: Below LOQ BIA 2-005 (main BIA 2-093 metabolite) LOQ= 10 ng/mL Plasma warfarin HPLC method with ultraviolet detection. LOQ: for S-warfarin assay was 0.025 mg/L. Accuracy S-warfarin: 97 – 115% Precision S-warfarin: 3.21 – 9.80% R-warfarin assay was 0.025 mg/L. Accuracy R-warfarin: 97 – 115% Precision R-warfarin: 3.30 – 9.71%
PK Assessment	Non-compartmental methods The following pharmacokinetic parameters for BIA 2-005, S-

	warfarin and R-warfarin: Cmax, Tmax, AUCt, Cmin, PTF, Tmin, T ½ For the evaluation of any significant pharmacokinetic interaction between BIA 2-093 and R- and S-warfarin, the parameters AUCt and Cmax were defined as primary variables.
Safety Assessment	Number, severity and relation to treatment of the adverse events reported; heart rate and blood pressure; 12-lead electrocardiogram; and clinical laboratory safety tests (hematology, plasma biochemistry, coagulation and urinalysis).
PD Assessment	INR measurements were used to assess any pharmacodynamic interaction between BIA 2-093 and Warfarin. Data analysis was based on the mean of the last three values for INR obtained from each phase of the study. A change in INR of 25% when BIA 2-093 was given concomitantly with warfarin was considered to be of at least borderline clinical importance. ANOVA was to be used to test for differences in the *Test* versus *References* means for INR values. An α-level of 0.05 was to be used. The 90%CI for the difference between the untransformed INR means was to be calculated, comparing *Test* versus *Reference* treatments.

Results:

BIA 2-005:
Mean concentration-time profile for BIA 2-005 is provided in the following figure:

Mean (SD) plasma BIA 2-005 concentration-time profile following an oral 7-day administration of 1200 mg BIA 2-093 once-daily (Day 8 – Phase B) (n=13).



Mean Cmin of BIA 2-005 at Days 2, 4, 6, 7 and 8 (Phase B) are presented in the following table. Steady state conditions were reached after day 4 of dosing.

Mean Cmin (pre-dose) of BIA 2-005 at Days 2, 4, 6, 7 and 8 (Phase B) following once-daily oral administration of 1200 mg BIA 2-093 with warfarin (n=13)

	Day 2	Day 4	Day 6	Day 7	Day 8
BIA 2-005 (ng/mL)	BLQ -	10919 (4792)	10427 (4123)	10541 (3474)	10060 (3340)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
BLQ – Below limit of quantification of the assay (10.0 ng/ml).

The mean steady-state pharmacokinetic parameters of BIA 2-005 following the last dose in which BIA 2-093 was concomitantly administered with warfarin (Day 8 of Phase B) are summarized in the following table.

Pharmacokinetic parameters of BIA 2-005 following an oral 7-day administration of BIA 2-093 1200 mg once-daily with warfarin (n=13)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng.h/mL)
BIA 2-005	31652 (11150)	6 (1-12)	411834 (113305)

Results of C_{max} and AUC_{τ} are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses. t_{max} values are median with range values in parentheses.

Maximum plasma concentrations (Cmax) of BIA 2-005 were reached (tmax) between 1 and 12 h post-dose (median of 6 h) and thereafter plasma BIA 2-005 concentrations declined with a mean apparent terminal half-life of 12.5 hours.

S-Warfarin:
Plasma levels of S-warfarin were assayed at pre-dose (Cmin) in the last 3 days of Phase A, to demonstrate that the steady-state of plasma warfarin concentrations had been achieved before commencing Phase B. Mean results are presented in the following table.

Mean Cmin (pre-dose) of S-warfarin in the 3 last days of Phase A (n=13)

	3 days before starting Phase B	2 days before starting Phase B	1 day before starting Phase B
S-warfarin (mg/L)	0.216 (0.0752)	0.219 (0.0710)	0.243 (0.0815)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.

Steady-state of S-warfarin concentrations was achieved before Day 1 of Phase B.

The mean steady-state pharmacokinetic parameters of S-warfarin following a once-daily individualized dose (Day 1 and Day 8 - Phase B) are summarized in following table

Pharmacokinetic parameters of S-warfarin following once-daily individualized warfarin dose in Phase B (n=13)

S-warfarin	C_{max} (mg/L)	t_{max} (h)	AUC_{τ} (mg.h/L)
Day 1	0.455 (0.149)	1 (0.5-4)	7.05 (2.40)
Day 8	0.375 (0.141)	1 (0.5-4)	5.56 (2.25)

Results of C_{max} and AUC_{τ} are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses. t_{max} values are median with range values in parentheses.

Maximum plasma concentrations (Cmax) of S-warfarin were reached (tmax) between 0.5 and 4 h post-dose (median of 1 h) for both Day 1 and Day 8 of Phase B. The extent of systemic exposure to S-warfarin was characterized by the mean Cmax and AUCt was lower on day 8 compared to day 1.

Plasma levels of S-warfarin were assayed at pre-dose (Cmin) at Days 3, 5, 7 and 8 of Phase C to assess whether BIA 2-093 affects trough levels of warfarin when it is removed from concomitant warfarin therapy. Trough levels of S-warfarin were not affected by the co-administration of BIA 2-093 and Warfarin.

Mean Cmin (pre-dose) of S-warfarin at Days 3, 5, 7 and 8 of Phase C (n=13)

	Day 3	Day 5	Day 7	Day 8*
S-warfarin (mg/L)	0.193 (0.0925)	0.200 (0.0760)	0.203 (0.0751)	0.216 (0.0798)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
* 24 h post last-warfarin dose.

R-Warfarin:

Plasma levels of R-warfarin were assayed at pre-dose (Cmin) in the last 3 days of Phase A, to demonstrate that the steady-state of plasma concentrations had been achieved. Mean results are presented in the following table. Steady-state of R-warfarin plasma concentrations was achieved before Day 1 of Phase B.
Mean Cmin (pre-dose) of R-warfarin in the 3 last days of Phase A (n=13)

	3 days before starting Phase B	2 days before starting Phase B	1 day before starting Phase B
R-warfarin (mg/L)	0.316 (0.140)	0.323 (0.141)	0.358 (0.147)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.

The mean pharmacokinetic parameters of R-warfarin following once-daily individualized dose (Day 1 and Day 8 of Phase B) are summarized in the following table.

Pharmacokinetic parameters of R-warfarin following once-daily individualized warfarin dose in Phase B (n=13)

R-warfarin	C_{max} (mg/L)	t_{max} (h)	AUC_{τ} (mg.h/L)
Day 1	0.575 (0.248)	1 (0.5-4)	9.93 (4.39)
Day 8	0.556 (0.248)	1 (0.5-8)	9.85 (4.54)

Results of C_{max} and AUC_{τ} are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses. t_{max} values are median with range values in parentheses.

Plasma levels of R-warfarin were assayed at pre-dose (Cmin) at Days 3, 5, 7 and 8 of Phase C to assess whether BIA 2-093 affects trough levels of warfarin when it is removed from concomitant warfarin therapy. BIA 2-093 does not affect the trough levels of R-warfarin when it is removed from concomitant warfarin therapy. Mean results are presented in the following table.

Mean Cmin (pre-dose) of R-warfarin at Days 3, 5, 7 and 8 of Phase C (n=13)

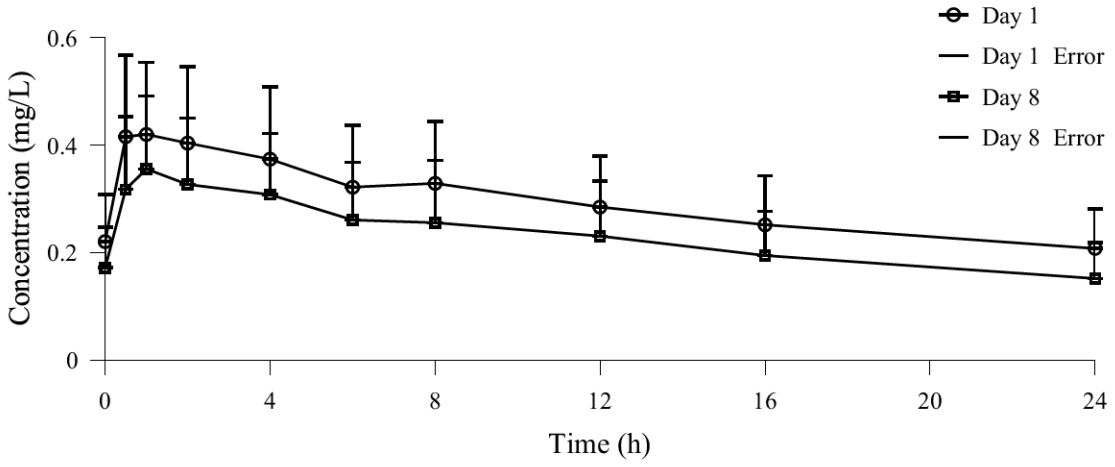
	Day 3	**Day 5**	**Day 7**	**Day 8***
R-warfarin (mg/L)	0.365 (0.199)	0.366 (0.207)	0.339 (0.162)	0.357 (0.169)

Results are expressed as arithmetic means with the corresponding standard deviations (SD) in parentheses.
* 24 h post last-warfarin dose.

Effect of BIA 2-093 on the main pharmacokinetic parameters of Warfarin"

Mean S-warfarin concentration-time profiles at Day 1 and 8 of Phase B following once daily individualized warfarin dose with 1200 mg BIA 2-093 are provided in the following figure.

Mean (SD) plasma S-warfarin concentration-time profiles following once daily individualized warfarin dose at Day 1 (*Reference*) and Day 8 (*Test*) (n=13)



The following table contains the point estimates and 90%CI for the comparison of Cmax and AUCt for warfarin.

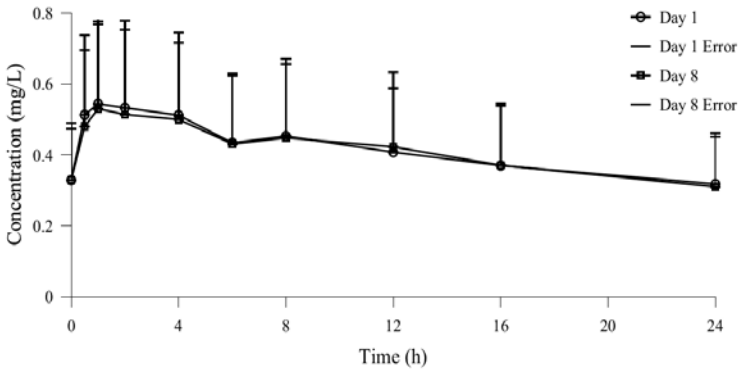
Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of Cmax and AUCt of S-warfarin at Day 1 (*Reference*) and Day 8 (*Test*) (n=13)

S-warfarin parameters		*Test / Reference*
C_{max}	PE	0.81
	90%CI	0.76,0.86
AUC_{τ}	PE	0.77
	90%CI	0.72,0.82

The 90% CI are not included within the 0.80-1.25 reference interval, and therefore bioequivalence was not proven for both pharmacokinetic parameters assessed. No statistically significant differences were found between tmax values for S-warfarin when Test and Reference were compared.

Mean steady-state R-warfarin concentration-time profiles at Day 1 and Day 8 of Phase B following once-daily individualized warfarin dose with 1200 mg BIA 2-093 are provided in the following figure.

Mean (SD) plasma R-warfarin concentration-time profiles following once daily individualized warfarin dose at Day 1 (Reference) and Day 8 (Test) (n=13)



The following table contains the PE and 90%CI for the comparison of Cmax and AUCt for R warfarin

Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of Cmax and AUCt of R-warfarin at Day 1 (Reference) and Day 8 (Test) (n=13)

R-warfarin parameters		*Test / Reference*
C_{max}	PE	0.97
	90%CI	0.91,1.02
AUC_{τ}	PE	0.98
	90%CI	0.92,1.04

The 90%CI are included within the 0.80,1.25 reference interval, and therefore bioequivalence was proven for both pharmacokinetic parameters assessed. No statistically significant differences were found between tmax values for R-warfarin when *Test* and *Reference* were compared.

Pharmacokinetic summary

S-warfarin AUCt and Cmax, parameters were significantly decreased by 23% and 19%, respectively following a 7-day treatment with BIA 2-093 1200 mg once-daily. With respect to R-warfarin AUCt and Cmax, no significant change in any of the pharmacokinetic parameters was found.

Pharmacodynamic Summary

No statistically significant differences were found for INR values under both conditions (with and without concomitant administration of BIA 2-093).

Mean INR values in Phases A, B and C (n=13)

	Phase A	**Phase B**	**Phase C**
Mean INR*	1.45	1.51	1.41
Standard deviation	0.102	0.249	0.246
90%CI	1.43,1.48	1.44,1.57	1.35,1.48

*Mean INR of the last 3 days of each phase.

Measurements of INR resulted in a mean ±SD of 1.45±0.10 when warfarin was used alone in Phase A (*Control*) and 1.51±0.25 when BIA 2-093 was added to warfarin in Phase B. In relation to Phase A, a slight mean INR increase of 4.04% was reported in Phase B, suggesting that BIA 2-093 was not expected to have significant clinical effect. In Phase C, following discontinuation of BIA 2-093 administration, a decrease of -5.42% in the INR was found.

Safety Summary

The sponsor reported that during the course of the study, 9 subjects reported a total of 32 adverse occurrences. The sponsor reported no clinically relevant abnormalities or

apparent trends were observed in vital signs during the study. There were no clinically relevant changes in body weight during study participation.

During the phase of the study in which BIA 2-093 was administered, 7 subjects reported a total of 17 adverse events, of which 6 were considered possibly related to treatment. All but one (lipothymia) were of mild intensity and all recovered without squealer.

Conclusion

In healthy subjects there was a small statistically significant effect of BIA 2-093 on the pharmacokinetics of S-warfarin, but no effect on R-warfarin was found. Despite that, no significant effect on the pharmacodynamic endpoint (INR) was found.

Reviewer comments: The reviewer agrees with the sponsor general conclusions. The decrease in warfarin exposure observed did not affect the pharmacodynamic endpoint of INR. It must be noted that the pre-defined INR range of 1.3 to 1.8 is usually sub-therapeutic.

Study 114: Effect of BIA 2-093 on the pharmacokinetics of a combined oral contraceptive in healthy female volunteers

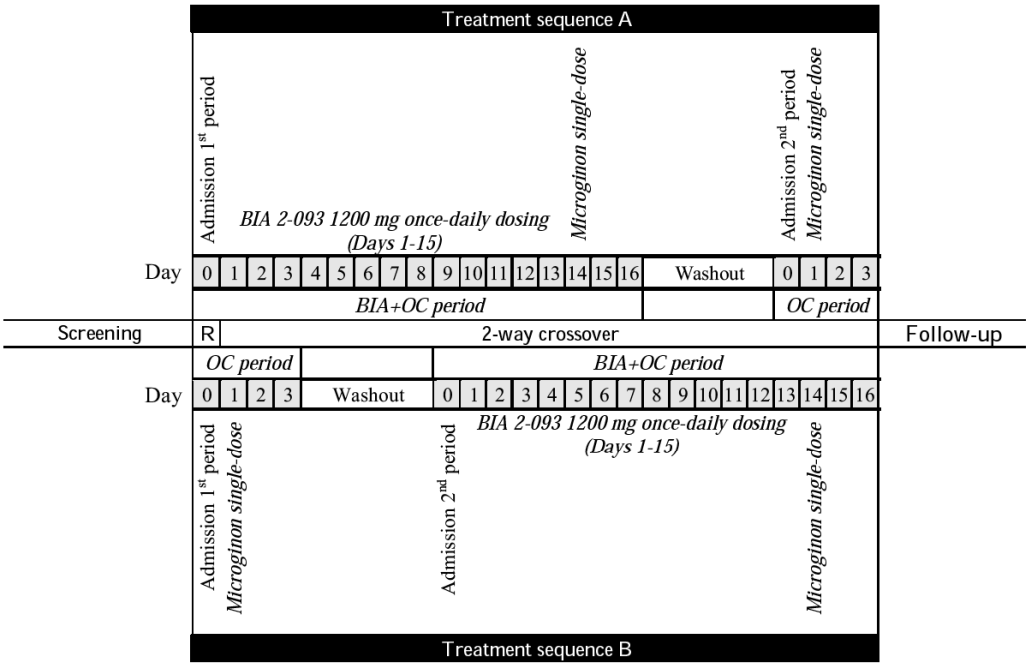
Objectives:
Primary: To investigate the effect of BIA 2-093 on oral contraceptive components (ethinyloestradiol and levonorgestrel) plasma concentration versus time profiles when administered concomitantly to healthy women.
Secondary: To assess the tolerability and safety of concomitant administration of BIA 2-093 and an oral contraceptive in healthy women.

The study design is as follows:

Study Design	Single center, two-way crossover, randomized, open-label study.
Study Population	N= 20; N= 17 for pharmacokinetic analysis Age: 18 to 40 years Gender: Pre-menopausal female Weight: 57 – 69 kg
Treatment groups	Oral contraceptive (OC) group OC + eslicarbazepine acetate (BIA 2-093) group BIA 2-093 600 mg tablets (Batch # 040121-L) Microginon® coated tablets containing 30 μg ethinyloestradiol and 150 μg levonorgestrel (Batch # 33811)
Dosage and Administration	OC Period: Single dose of Microginon on day 1 OC + BIA 2-093 Period: 1200 mg (2 tablets of 600 mg) once daily on days 1 -15 plus single dose of Microginon on day 14 For OC doses: At least 8-hours overnight fast BIA 2-093: Administered without regard to time of meal. Washout Treatments were separated by at least 3 weeks
Sampling: Blood	For Plasma BIA 2-094 (eslicarbazepine) Assay Pre-dose on days 1, 2, 4, 6, 8, 10, 12, 14, 15 For Plasma OC Assay Pre-dose, ½ h, 1 h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 36h, 48 post-dose
Analysis	For BIA 2-194 LC-MS/MS LLOQ: 50 ng/mL Calibration range: 50 – 1000 ng/mL Precision: 1.3 – 3.7% Accuracy: 91.3 – 108.7% For levonorgestrel and ethinyloestradiol LC-MS/MS

	LLOQ for levonorgestrel: 0.05 ng/mL Calibration range: 0.05 – 10 ng/mL, QC 0.05, 0.14, 4.0, 8 ng/ml Precision: 1.3 – 7.7% Accuracy: 93.8 – 103.3% LLOQ for ethinyloestradiol: 3 pg/mL Calibration range: 3 – 300 pg/mL, QC, 3, 8.4, 120, 240 pg/ml Precision: 0.9-6.9% Accuracy: 96.7 – 106.7%
PK Assessment	Cmax, AUC(0-24h), AUC(0-t), AUC(0-∞), T ½
Safety assessment	Vital signs, ECG, Neurological exam, physical history, physical exam, clinical laboratory, AEs
PD Assessment	None

Study design diagram



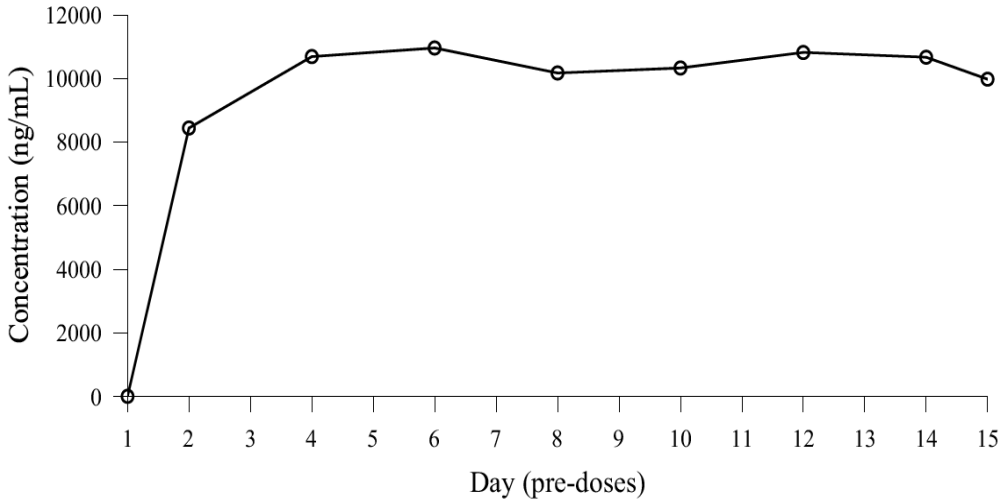
R = Randomisation
- On Days 1-13 of the BIA+OC period, subjects should attend the research facilities early in the morning for BIA 2-093 administration.
- On the evening of Day 0 of the OC period and of Day 13 of the BIA+OC period, subjects were to be admitted at UFH and remained under clinical supervision until at least 48 h post Microginon® single-dose (on Days 1 and 14, respectively).
BIA = BIA 2-093; OC = Oral Contraceptive (Microginon®)

Pharmacokinetic Results:

Mean concentration-time profiles for BIA 2-194, levonorgestrel and ethinyloestradiol are provided in the following figures.

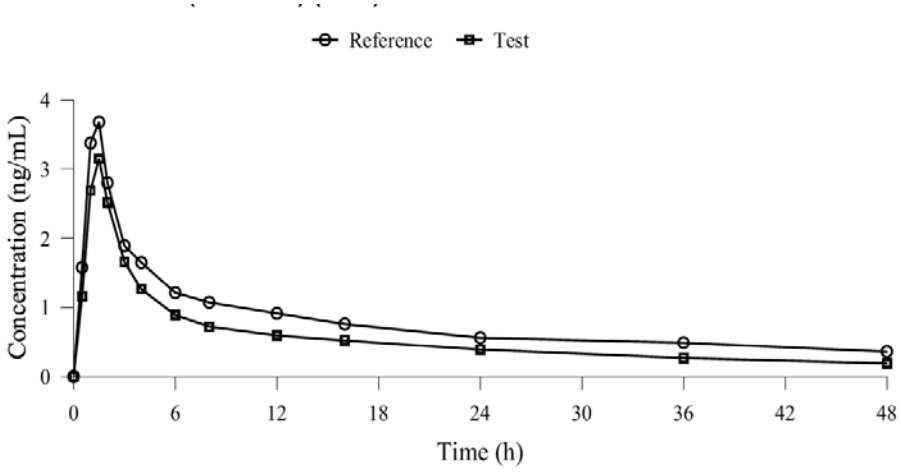
Eslicarbazepine (BIA 2-194)

Mean trough plasma BIA 2-194 concentration-time profile over a 15-day oral regimen of BIA 2-093 1200 mg once-daily in which the 14th dose was administered concomitantly with a single-dose of Microginon® (n=17)



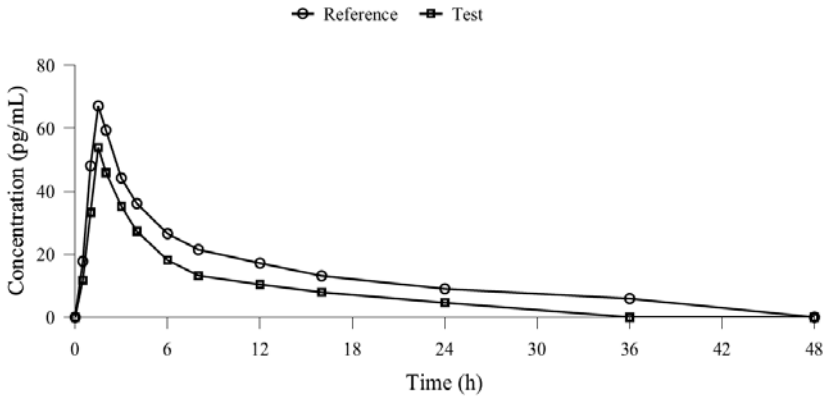
Levonorgestrel:

Mean plasma Levonorgestrel concentration-time profile following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once-daily (Test) and following administration of a single-dose of Microginon® administered alone (Reference) (n=17)



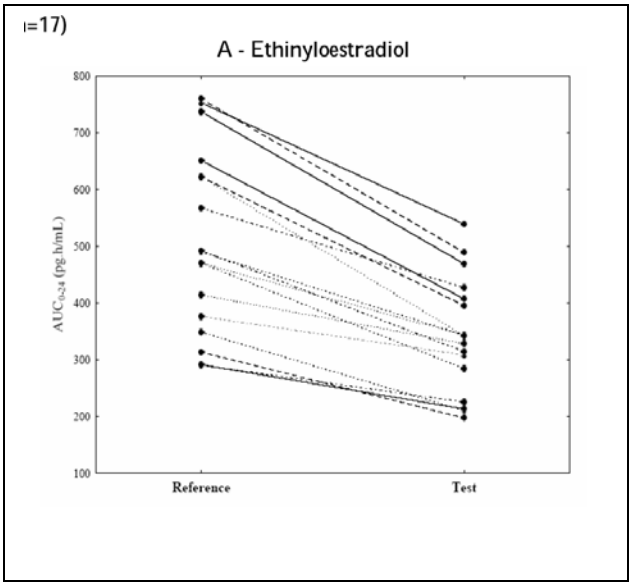
Ethinylestradiol

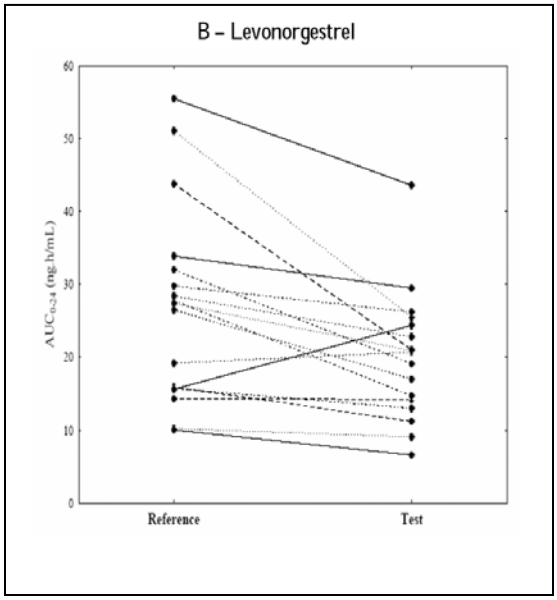
Mean plasma Ethinyloestradiol concentration-time profile following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once-daily (Test) and following administration of a single-dose of Microginon® administered alone (Reference) (n=17)



The following figure presents the effect of eslicarbazepine on the individual AUC (0-24) results of ethinyloestradiol and levonorgestrel obtained in the reference and test periods.

Individual AUC(0-24) of ethinyloestradiol (A) and levonorgestrel (B) following a single-dose of Microginon® administered concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once-daily (Test) and following a single-dose of Microginon® administered alone (Reference)
(n=17)





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Mean results of trough concentrations of eslicarbazepine on days 1, 2, 4, 6, 8, 10, 12, 14 and 15.

Mean trough (pre-dose) plasma concentrations of BIA 2-194 on Days 1, 2, 4, 6, 8, 10, 12, 14 and 15 during a 15-day oral regimen of BIA 2-093 1200 mg once-daily (n=17)

	Study Day								
	1	2	4	6	8	10	12	14	15
n	17	17	17	17	17	17	17	17	17
Mean (ng/mL)	0.00	8443	10691	10961	10175	10332	10821	10670	9978
SD (ng/mL)	-	1422	1736	1737	996	1470	1806	1447	1452
CV(%)	-	16.8	16.2	15.8	9.79	14.2	16.7	13.6	14.6

n = Number of subjects; Mean = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Steady-state trough (i.e., pre-dose) plasma concentrations of BIA 2-194 were reached approximately within 4 days of dosing and remained stable during the remaining eslicarbazepine acetate dosing of the BIA 2-093 + OC period.
The pharmacokinetic parameters of ethinylestradiol and levonorgestrel following administration of the administration of a single dose of Microginon concomitantly with the 14th dose and following a single dose of Microginon administered alone are presented in the following tables.

Ethinylestradiol:
Mean pharmacokinetic parameters of ethinyloestradiol following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once-daily (Test) and following administration of a single-dose of Microginon® administered alone (Reference) (n=17)

Test

	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	AUC_{0-24} (pg.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
n	17	17	17	17	17	17	17
Gmean	53.4	1.67	347	416	329	0.0643	10.8
Amean	56.3	1.74	374	446	343	0.0719	11.8
SD	17.9	0.53	145	168	102	0.0387	4.83
CV%	31.8	30.8	38.9	37.6	29.6	53.8	40.9
Median	52.9	1.50	343	451	342	0.0554	12.5
Minimum	22.9	1.00	185	211	197	0.0318	3.88
Maximum	91.4	3.00	654	789	539	0.179	21.8

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Reference

	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	AUC_{0-24} (pg.h/mL)	λ_z (1/h)	$t_{1/2}$# (h)
n	17	17	17	17	17	17	17
Gmean	66.1	1.52	595	701	485	0.0426	16.3
Amean	68.6	1.53	639	754	510	0.0445	16.9
SD	19.1	0.21	243	293	161	0.0142	4.65
CV%	27.8	14.0	38.0	38.9	31.5	31.9	27.5
Median	71.5	1.50	612	752	490	0.0426	16.3
Minimum	37.8	1.00	313	368	290	0.0279	8.53
Maximum	107	2.00	1072	1394	760	0.0812	24.8

= Unreliable value; period over which rate constant was calculated was < 2 times the resulting half-life in several subjects; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Levonorgestrel

Mean pharmacokinetic parameters of Levonorgestrel following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once-daily (Test) and following administration of a single-dose of Microginon® administered alone (Reference) (n=17)

Test

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
n	17	17	17	17	17	17	17
Gmean	3.22	1.28	24.0	29.4	18.2	0.0328	21.1
Amean	3.43	1.38	26.6	32.3	20.0	0.0332	21.4
SD	1.33	0.49	12.1	14.3	8.81	0.0052	3.34
CV%	38.9	35.1	45.6	44.2	44.1	15.7	15.6
Median	3.30	1.50	27.4	31.8	20.7	0.0332	20.9
Minimum	1.58	0.50	8.44	11.2	6.58	0.0250	15.8
Maximum	7.39	2.00	58.4	68.2	43.6	0.0439	27.8

= Unreliable value; period over which rate constant was calculated was systematically < 2 times the resulting half-life; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

Reference

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-24} (ng.h/mL)	λ_z (1/h)	$t_{1/2}^{\#}$ (h)
n	17	17	17	17	17	17	17
Gmean	3.72	1.21	33.6	46.7	23.8	0.0239	28.9
Amean	3.99	1.26	38.3	52.7	26.9	0.0243	29.4
SD	1.54	0.36	20.0	26.9	13.6	0.00403	5.29
CV%	38.5	28.4	52.1	50.9	50.4	16.6	18.0
Median	3.63	1.50	39.3	51.7	27.4	0.0249	27.8
Minimum	1.76	0.50	14.1	22.1	10.0	0.0176	23.0
Maximum	7.32	2.00	76.5	104	55.5	0.0302	39.4

= Unreliable value; period over which rate constant was calculated was systematically < 2 times the resulting half-life; n = Number of subjects; G_{mean} = Geometric mean; A_{mean} = Arithmetic mean; SD = Standard deviation; CV = Coefficient of variation

The following table contains the statistical comparison (point estimates and 90% CI) of Cmax and AUC of ethinylestradiol and levnorgestrel.

Point estimates (PE) and 90% confidence intervals (90%CI) for the comparison of Cmax and AUC0-24 of levonorgestrel and ethinyloestradiol following administration of a single-dose of Microginon® concomitantly with the 14th dose of a 15-day oral regimen of BIA 2-093 1200 mg once daily (Test) and following administration of a single-dose of Microginon® administered alone (Reference)

Parameters		*Test / Reference*	
		Ethinyloestradiol	Levonorgestrel
C_{max}	PE	0.80	0.87
	90%CI	0.71; 0.92	0.79; 0.95
AUC_{0-24}	PE	0.68	0.76
	90%CI	0.64; 0.71	0.68; 0.86
$AUC_{0-\infty}$	PE	0.58	0.63
	90%CI	0.55; 0.62	0.55; 0.72

The Cmax of levonorgestrel Test/Reference ratio presented a point estimate (PE) of 0.87 and a 90%CI of 0.79-0.95. The AUC(0-24) Test/Reference ratio presented a PE of 0.76 and a 90%CI of 0.68-0.86. The AUC(0-∞) Test/Reference ratio presented a PE of 0.63 and a 90%CI of 0.55-0.72. The 90%CI are not included within the 0.80-1.25 reference interval. Therefore bioequivalence was not proven for levonorgestrel Cmax and AUC(0-24) and AUC(0-∞).

The Cmax of esthinylestradiol Test/Reference ratio presented a PE of 0.80 and a 90%CI of 0.71-0.92. The AUC(0-24) Test/Reference ratio presented PE of 0.68 and a 90%CI of 0.64-0.71. The AUC(0-∞) Test/Reference ratio presented PE of 0.58 and a 90%CI of 0.55 – 0.62. The 90%CI are not included within the 0.80-1.25 reference interval, and therefore bioequivalence was not proven for ethinylestradiol Cmax and AUC(0-24) and AUC(0-∞).

Pharmacokinetic conclusions

Exposure to levonorgestrel and ethinyloestradiol, as reflected by the Cmax and the AUC does not fit the claim of bioequivalence between Test (Microginon® plus eslicarbazepine acetate) and Reference (Microginon® alone), because the 90%CI fall outside the reference interval of 0.8 to 1.25. No statistical differences were found between tmax values for levonorgestrel and ethinyloestradiol when Test and Reference were compared.

Exposure to eslicarbazepine acetate decreased the ethinyloestradiol Cmax, AUC(0-24) and AUC(0-∞). Levonorgestrel Cmax, AUC(0-24) and AUC(0-∞) were also decreased. The eslicarbazepine acetate effect on the mean ethinylestradiol AUC(0-24) was higher than on the mean levonorgestrel AUC (0-24) (33% versus 26%, respectively).

Eslicarbazepine Acetate shares with Oxcarbazepine (Trileptal®, Novartis) the same active metabolites (S-licarbazepine and R-licarbazepine) although in different proportions. The sponsor reports that similar results were reported with Trileptal® and the mostly likely explanation is that the decrease in plasma ethinyloestradiol and levonorgestrel was due to induction of the CYP3A4 isoenzymes involved in their oxidation.

Safety summary

The sponsor reported that during the study, 19 subjects reported a total of 93 treatment-emergent adverse events. From these 93 adverse events 86 were reported during the sixteen days treatment period of BIA 2-093 + Microginon® and the remaining 7 adverse events were reported during the three days treatment period of Microginon®. Seventy-six adverse events (reported by 19 subjects) were considered to be possibly or definitely related with treatment. Seventeen (18.3%) were considered not related to treatment. The sponsor reported that with respect to the severity (intensity) of adverse events, 88 (94.6%) adverse events were mild in intensity. Two adverse events (somnolence + dizziness + concentration impairment and viral infection) were assessed as severe in intensity. The most common treatment-emergent adverse event was somnolence, followed by, dizziness and constipation.

Conclusions

The mean levonorgestrel Cmax decreased 13% (Test/Reference PE = 0.87; 90%CI = 0.79-0.95) and AUC(0-24) decreased 24% (PE = 0.76; 90%CI = 0.68-0.86) following administration of eslicarbazepine acetate. The mean Cmax ethinyloestradiol decreased 20% (Test/Reference PE = 0.80; 90%CI = 0.79-0.95) and AUC(0-24) decreased 32% (PE = 0.76; 90%CI = 0.68-0.86) following administration of eslicarbazepine acetate. No statistically significant differences were found between tmax values for levonorgestrel and ethinyloestradiol following administration of eslicarbazepine acetate. The sponsor concluded that the study showed that concomitant administration of eslicarbazepine acetate with hormonal contraceptives may render these contraceptives less effective.

Reviewer Comments: The reviewer agrees with the sponsor's conclusions.

Study 119: A Phase 1, Open-Label Drug Interaction Study Between Eslicarbazepine Acetate 1200 mg and Lamotrigine 150 mg Following Multiple Dose Administrations in Healthy Male Volunteers

Objectives

Primary: 1) To evaluate the effect of eslicarbazepine acetate (ESL) on the pharmacokinetics of Lamotrigine (LMT) at steady-state. 2) To evaluate the effect of Lamotrigine (LMT) on the pharmacokinetics of eslicarbazepine acetate (ESL), BIA 2-194 and BIA 2-195 at steady-state.

Secondary: To assess the safety and tolerability of ESL and LMT when each drug was administered alone or in combination in healthy male volunteers following a multiple dose administration.

The study design is as follows.

Study Design	Single center, multiple doses, open-label, two parallel study groups each receiving two formulations in a one-sequence design.
Study Population	Planned: 32 Analyzed and considered in statistical analysis Group A: 14; Group B: 14 Age: 36 ± 6 years Weight: Mean ± sd: 78.5 ± 9.4 kg
Treatment Groups + Dosage and Administration	Days 1 to 2 (Up-Titration) Group A: 600 mg once daily dose of ESL administered orally with 240 mL water in the morning for 2 consecutive days. Group B: 50 mg (2 x 25 mg tablets) once daily dose of LMT administered with 240 mL of water in the morning for 2 consecutive days Days 3 to 8 Group A: 1200 mg (2x 600 mg tablets) of ESL once daily was administered in the morning for 6 consecutive days Group B: 150 mg once daily oral dose of LMT with 240 mL of water in the morning for 6-consecutive days Days 9 to 10 (Up-Titration) Group A: Concomitant doses of ESL 1200 mg and LMT 50 mg orally administered in morning for 2 consecutive days Group B: Concomitant doses of ESL 1200 mg and LMT 150 mg administered in the morning for 2 consecutive days Days 11 to 27 Groups A + B: Concomitant doses of ESL 1200 mg and LMT 150 mg administered once daily in the morning for 17 consecutive days. At each dosing drug was administered with 240 mL of drug Eslicarbazepine Acetate 600 mg (BIA 2-093) Batch no. 050059-L Lamotrigine (Lamictal®) 150 mg, Batch no. 6ZM5569

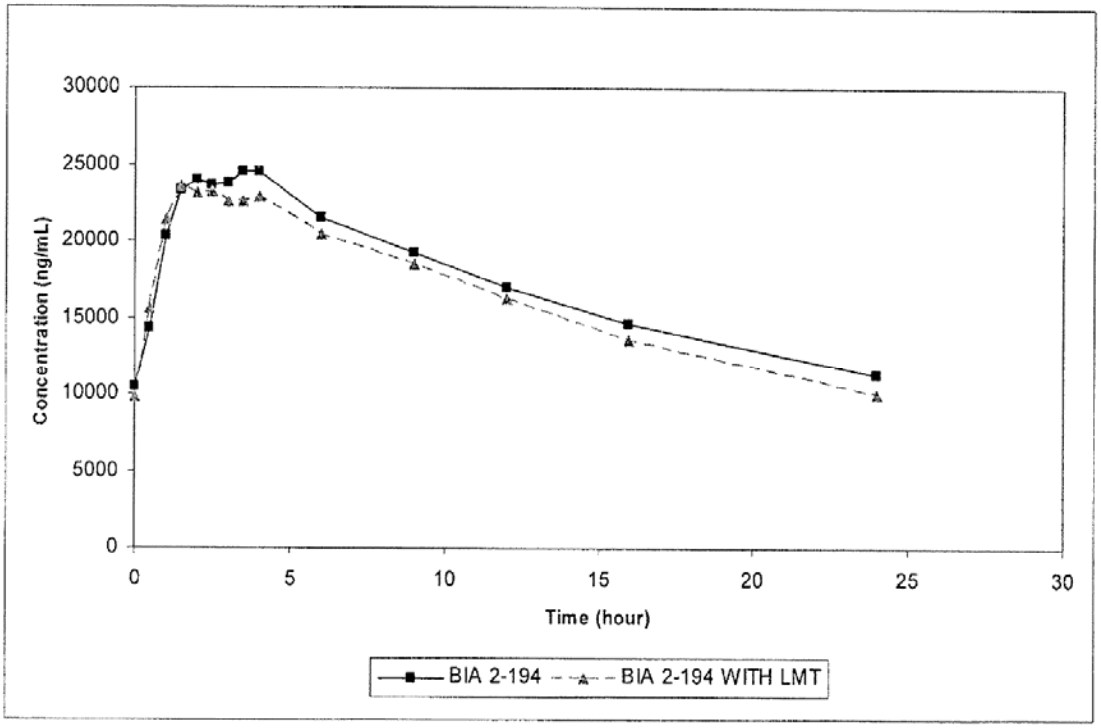
	Lamotrigine (Lamictal) 25 mg, Batch no. 6ZM5564 Diet: At least 10 hour overnight fast
Dosage and Admin.	Refer to Treatment groups
Sampling	PK of ESL (Group A) Day 8: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration Day 27:Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration PK of LMT (Group B) Day 8: Pre-dose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3,4,6,9,12, 16 and 24 hours post dose Day 27: Pre-dose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 16 and 24 hours post dose
Analysis	ESL, BIA 2-194 and BIA 2-195 LC/MS/MS Assay range: ESL: 50 to 1000 ng/mL BIA 2-194 and BIA 2-195: 50 to 25000 ng/mL Quality control concentrations: 50, 140, 10000, 20000 ng/mL Precision: %CV< 20% at LLOQ and < 15% at Quality control; Accuracy: 94.1 – 108.4% Lamotrigine HPLC with MSD detection Assay Range: 5 to 1500 ng/mL Quality control concentrations: 0.600, 1.800, 3.500, 9.000 µg/mL Precision (%CV): 4.5- 8.6% Accuracy: 90.3 – 103.6%
PK Assessment	Cmin, Cmax, AUCt, Tmax, Fluctuation, Kel and T ½ 2-sided 90% confidence interval (CI) of the geometric means (Day 27 to Day 8) for the Cmin, Cmax, AUCt.
Safety	Adverse events, physical examination, standard laboratory parameters, 12-lead ECG, neurological function tests and neurological signs
PD Assessment	None

Results

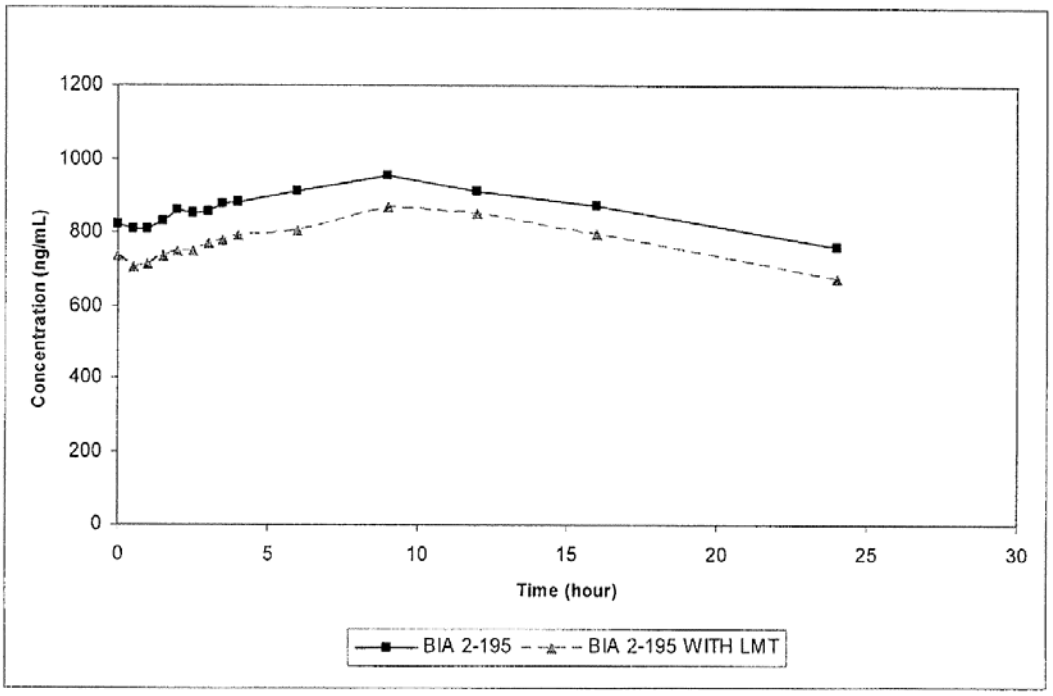
BIA 2-194 and BIA 2-195:

Plasma concentration of BIA 2-093 derived from the administration of the BIA 2-093 with Lamotrigine (Day 27) and BIA 2-093 alone (Day 8) was at BLQ. The mean measured plasma concentration versus time profile for BIA 2-194 and BIA 2-195 are provided in the following figure.

Linear Profile of Mean BIA 2-194 Concentrations



Linear Profile of Mean BIA 2-195 Concentrations



The mean pharmacokinetic profiles indicate that co-administration of eslicarbazepine acetate (BIA 2-093) with lamotrigine results in similar profiles of eslicarbazepine (BIA 2-194) and an apparent decrease in BIA 2-195 concentrations.

A summary of the pharmacokinetic parameters for the metabolites eslicarbazepine (BIA 2-194) and BIA 2-195 and the statistical analysis are presented in the following tables

Summary of Mean Pharmacokinetic Parameters for Eslicarbazepine (BIA 2-194)

PARAMETER	BIA 2-194 WITH LMT		BIA 2-194		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	9706	16.9	10317	10.4	4.81	<0.05
ln (C_{min}) (ng/mL)	9.1686	1.7	9.2367	1.1	6.46	<0.05
C_{max} (ng/mL)	25579	22.2	26771	17.6	1.09	N.S.
ln (C_{max}) (ng/mL)	10.1251	2.3	10.1809	1.7	1.61	N.S.
T_{max} (hours) §	2.00	73.1	2.00	48.1	0.03	N.S.
AUC_τ (ng·h/mL)	391231	15.1	407110	15.3	2.02	N.S.
ln (AUC_τ) (ng·h/mL)	12.8667	1.2	12.9056	1.2	1.40	N.S.
K_{el} ($hour^{-1}$)	0.0404	17.7	0.0373	15.6	5.62	<0.05
$T½_{el}$ (hours)	17.68	17.2	19.04	16.5	5.26	<0.05
Fluctuation (%)	96.19	27.0	97.74	25.8	0.05	N.S.
ln (Fluctuation) (%)	4.5313	6.1	4.5537	5.4	0.10	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-194 with 90% CI

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-194 with LMT to BIA 2-194 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-194 WITH LMT	BIA 2-194		LOWER	UPPER
C_{min}	7.1	9591	10267	93.42	89.09	97.96
C_{max}	11.7	24962	26393	94.58	87.49	102.24
AUC_τ	8.7	387213	402545	96.19	90.76	101.95
Fluctuation	18.6	92.88	94.98	97.79	86.44	110.63

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

Summary of Pharmacokinetic Parameters for BIA 2-195

PARAMETER	BIA 2-195 WITH LMT		BIA 2-195		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	664	21.3	740	23.4	20.62	<0.001
ln (C_{min}) (ng/mL)	6.4772	3.4	6.5794	3.7	26.35	<0.001
C_{max} (ng/mL)	889	21.6	966	24.0	4.54	<0.10
ln (C_{max}) (ng/mL)	6.7689	3.2	6.8468	3.5	5.43	<0.05
T_{max} (hours) §	9.00	32.3	9.00	35.3	2.02	N.S.
AUC_τ (ng·h/mL)	18805	21.6	20488	26.1	4.82	<0.05
ln (AUC_τ) (ng·h/mL)	9.8202	2.2	9.8930	2.8	2.78	N.S.
Fluctuation (%)	28.69	24.3	26.88	24.1	0.73	N.S.
ln (Fluctuation) (%)	3.3287	7.4	3.2629	7.8	0.63	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-195 with 90% CI

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-195 with LMT to BIA 2-195 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-195 WITH LMT	BIA 2-195		LOWER	UPPER
C_{min}	5.3	650	720	90.28	87.15	93.52
C_{max}	8.9	870	941	92.51	87.19	98.15
AUC_τ	11.6	18401	19790	92.98	86.07	100.45
Fluctuation	22.1	27.90	26.12	106.80	92.26	123.64

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

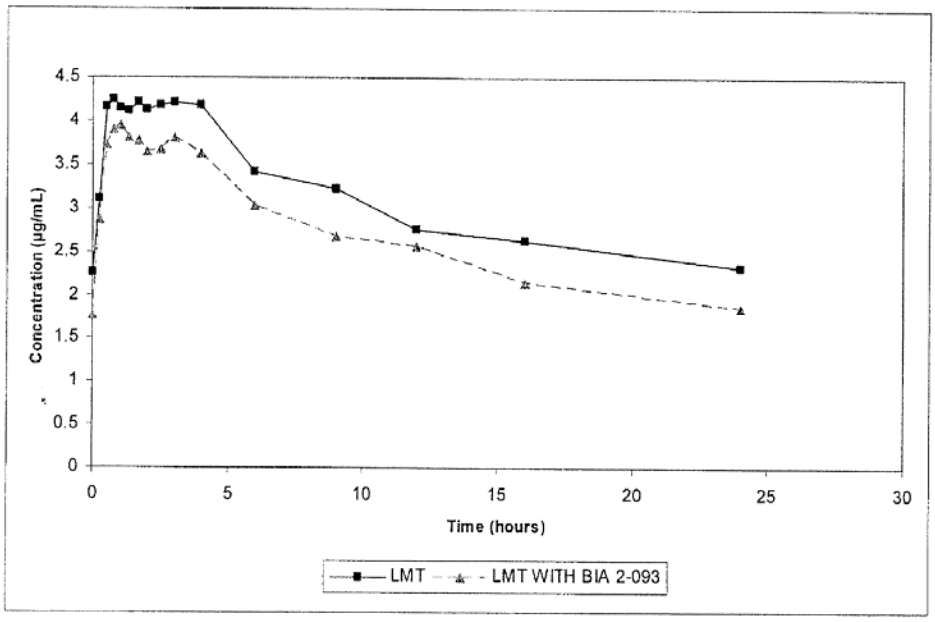
The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-194 with LMT to BIA 2-194 alone, are within the pre- specified 80% to 125% equivalence range.

The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-195 with LMT to BIA 2-195 alone, are within the pre- specified 80% to 125% bioequivalence range.

Lamotrigine

The mean measured plasma concentration versus time profile of Lamotrigine (LMT), derived from the administration of LMT alone and LMT with BIA 2-093, is depicted in the following figure.

Linear Profile of Mean Lamotrigine Concentration



There is an apparent decrease in mean concentrations of LMT when it was administered with BIA 2-093 relative to LMT alone.

The pharmacokinetic parameters of interest and the statistical analysis are presented in the following tables

Summary of Mean Lamotrigine Pharmacokinetic Parameters

PARAMETER	LMT WITH BIA 2-093		LMT		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (µg/mL)	1.738	27.8	2.141	30.6	9.98	<0.01
ln (C_{min}) (µg /mL)	0.5175	53.2	0.7187	42.1	8.93	<0.05
C_{max} (µg /mL)	4.273	16.2	4.900	20.2	10.47	<0.01
ln (C_{max}) (µg /mL)	1.4402	11.3	1.5704	12.9	10.40	<0.01
T_{max} (hours) §	1.00	78.4	1.17	77.7	0.08	N.S.
AUC_{τ} (µg ·h/mL)	63.050	18.7	73.723	21.9	16.68	<0.01
ln (AUC_{τ}) (µg ·h/mL)	4.1287	4.3	4.2792	4.9	16.84	<0.01
K_{el} ($hour^{-1}$)**	0.0360	29.0	0.0350	42.0	0.04	N.S.
$T½_{el}$ (hours)**	20.73	27.2	22.64	36.1	0.49	N.S.
Fluctuation (%)	99.59	33.3	92.40	31.7	0.93	N.S.
ln (Fluctuation) (%)	4.5567	6.6	4.4798	7.1	0.91	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
** n= 11; subject 014, 022 and 026 were excluded from this particular statistical comparison.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Lamotrigine Pharmacokinetic Parameters

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		LMT with BIA 2-093 to LMT RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		LMT WITH BIA 2-093	LMT		LOWER	UPPER
C_{min}	18.0	1.678	2.052	81.77	72.58	92.13
C_{max}	10.7	4.221	4.808	87.79	81.74	94.30
AUC_{τ}	9.7	62.099	72.184	86.03	80.62	91.80
Fluctuation	21.6	95.26	88.22	107.98	93.61	124.57

* units are µg/mL for C_{min} and C_{max}, µg·h/mL for AUC_{τ} and % for Fluctuation.

The results demonstrate that the 90% confidence interval for Cmax geometric LSmeans of LMT with BIA 2-093 to LMT alone is within the pre-specified 80 to 125% equivalence range. And the results also indicate that the 90% confidence interval for AUC, geometric LSmeans of LMT with BIA 2-093 to LMT alone, is within the pre-specified 80 to 125% equivalence range. Cmin geometric LSmeans of LMT with BIA 2-093 to LMT alone is not contained within the pre-specified 80 to 125% equivalence range.

Pharmacokinetic Summary and Conclusions

The 90% confidence interval of the exponential of the ln-transformed Cmax and AUC, for BIA 2-194 with LMT versus BIA 2-194 alone were both within the bioequivalence acceptance range of 80 -125% for BIA 2-194 at steady-state.

The 90% confidence interval of the exponential of the In-transformed Cmax and AUC for BIA 2- 1 95 with LMT versus BIA 2- 195 alone were both within the bioequivalence acceptance range of 80-125% for BIA 2-195 at steady-state.

These results thus show that there was a no statistically significant impact of Lamotrigine on the pharmacokinetic properties of BIA 2-194 and BIA 2-195 when using a bioequivalence approach.

The 90% confidence interval of the exponential of the Ln-transformed Cmax and AUC, for LMT with BIA 2-093 versus LTM alone were both within the bioequivalence acceptance range of 80-125% for LTM at steady-state. The results also show that there was no statistically significant impact of BIA 2-093 on the AUC and Cmax of LMT when using a bioequivalence approach. Cmin of Lamotrigine decreased about 19% when LMT was added to BIA 2-093. This decrease in Cmin was significant.

The bioavailability of BIA 2-194 and BIA 2-195 at steady-state was equivalent to BIA 2-194 and BIA 2-195 in the presence of lamotrigine. The bioavailability of lamotrigine at steady-state was equivalent to lamotrigine in the presence of eslicarbazepine acetate.

Safety Summary

The sponsor reported that 27 subjects participating in the trial reported adverse events throughout the course of the study. None of these events were considered to be serious. Nine (9) subjects experienced 5 adverse events (infected insect bite, hypersensitivity, toothache, headache, anxiety) that required the use of concomitant medication.

Twenty-seven (27) of the thirty-two (32) subjects experienced at least one adverse event. A total of one hundred and fifty-nine (159) adverse events were reported during the study (average of 5.0 adverse events per subject). Among the sixteen (16) subjects of group A, thirteen (13) subjects experienced a total of 85 adverse events (average of 5.3 per subject). Among the 16 subjects of group B, fourteen (14) subjects experienced a total of 74 adverse events (average 4.6 per subject).

The sponsor reported that hypersensitivity reaction is most likely attributable to lamotrigine. Volunteers #004 and #023 suffered from hypersensitivity reaction and were withdrawn from the study. The sponsor reported that the sodium values encountered at the post study, despite the mild decrease were still clinically significant. The sponsor stated that when epileptic patients are practicing a physical activity under warm conditions, it could lower even more the bold sodium concentration, giving a rise to hyponatremic symptomatology. Whether this was caused by lamotrigine, eslicarbazepine, or the combination of both, is unclear.

The sponsor reported that it appears that the lamotrigine or the combination of lamotrigine/eslicarbazepine is more responsible for the observations of reduced sodium than the eslicarbazepine alone.

The sponsor reported that the sum of the expected average number of adverse events of subjects receiving eslicarbazepine acetate alone and those receiving lamotrigine alone was comparable to the observed average number of adverse events for subjects receiving eslicarbazepine acetate combined with lamotrigine. Therefore, no clinical interaction appears to be present in terms of adverse events when giving both drugs concomitantly.

Reviewer comments: The reviewer agrees with the conclusions of the sponsor. A pharmacokinetic interaction was not observed when eslicarbazepine is co-administered with lamotrigine.

Study 120: A Phase 1, Open-Label Drug Interaction Study Between Eslicarbazepine Acetate 1200 mg and Topiramate 200 mg Following Multiple Dose Administrations in Healthy Male Volunteers

Objectives

Primary: 1) To evaluate the effect of eslicarbazepine acetate (ESL) on the pharmacokinetics of Topiramate (TPM) at steady-state. 2) To evaluate the effect of Topiramate (TPM) on the pharmacokinetics of eslicarbazepine acetate (ESL), BIA 2-194 and BIA 2-195 at steady-state.

Secondary: To assess the safety and tolerability of ESL and TPM when each drug was administered alone or in combination in healthy male volunteers following a multiple dose administration.

The study design is as follows.

Study Design	Single center, multiple doses, open-label, two parallel study groups each receiving two formulations in a one-sequence design.
Study Population	Planned: 32 Analyzed and considered in statistical analysis Group A: 13; Group B: 14 Age (mean P SD): 34 ± 8 years Weight (Mean ± sd): 76.1 ± 8.9 kg
Treatment Groups + Dosage and Administration	Days 1 to 2 (Up-Titration) Group A: 600 mg once daily dose of ESL administered orally with 240 mL water in the morning for 2 consecutive days. Group B: 100 mg once daily dose of TPM administered with 240 mL of water in the morning for 2 consecutive days Days 3 to 4 (Up-Titration) Group B: 100 mg twice daily of TPM was orally administered (in the morning and in the evening) for a total of 200 mg daily dose, for 2 consecutive days Days 3 to 8 Group A: 1200 mg (2x 600 mg tablets) of ESL once daily was administered in the morning for 6 consecutive days Days 5 to 8 Group B: 200 mg once daily oral dose of TPM with 240 mL of water in the morning for 4-consecutive days Days 9 to 10 (Up-Titration) Group A: Concomitant doses of ESL 1200 mg and TPM 100 mg orally administered in morning for 2 consecutive days Group B: Concomitant doses of ESL 600 mg and TPM 200 mg administered in the morning for 2 consecutive days

	Days 11 to 12 (Up-Titration) Group A: Concomitant doses of ESL 1200 mg and TPM 100 mg was orally administered in the morning. In the evening a dose of 100 mg of TPM was orally administered for a total of 200 mg daily dose of TPM, for 2 consecutive days. Days 11 to 27 Groups B: Concomitant doses of ESL 1200 mg and TPM 200 mg administered once daily in the morning for 17 consecutive days. Days 13 to 27: Group A: Concomitant doses of ESL 1200 mg and TPM 200 mg was orally administered in the morning for 15 consecutive days. Each drug was administered with 240 mL of water Eslicarbazepine Acetate 600 mg (BIA 2-093) Batch no. 050059-L Topiramate (Topamax®) 200 mg, Batch no. 05FS129A Topiramate (Topamax) 100 mg, Batch no. 05HS015 Diet: At least 10 hour overnight fast
Dosage and Admin.	Refer to Treatment groups
Sampling	PK of ESL (Group A) Day 8: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration Day 27: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration PK of TPM (Group B) Day 8: Pre-dose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3,4,6,9,12, 16 and 24 hours post dose Day 27: Pre-dose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 16 and 24 hours post dose
Analysis	ESL, BIA 2-194 and BIA 2-195 LC/MS/MS Assay range: ESL: 50 to 1000 ng/mL BIA 2-194 and BIA 2-195: 50 to 25000 ng/mL Quality control concentrations: 150, 4500, 20000 ng/mL Precision (%CV) ≤ 20%, Accuracy: 94.6 to 103.6% Topiramate HPLC with MSD detection Assay Range: 0.10 to 10 μg/mL Quality control concentrations: 0.3, 4.5, 8 μg/mL Precision (%CV): 1.3 – 8.4%; Accuracy: 96.1 – 100.4%
PK Assessment	Cmin, Cmax, AUCt, Tmax, Fluctuation, Kel and T ½ 2-sided 90% confidence interval (CI) of the geometric means (Day 27 to Day 8) for the Cmin, Cmax, AUCt.

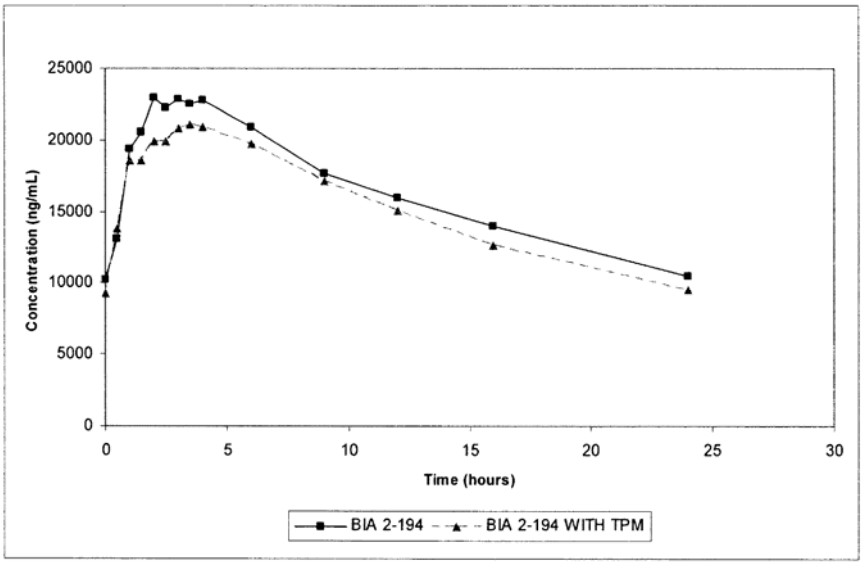
Safety	Adverse events, physical examination, laboratory parameters, 12-lead ECG, neurological function tests and neurological signs
PD Assessment	None

Results

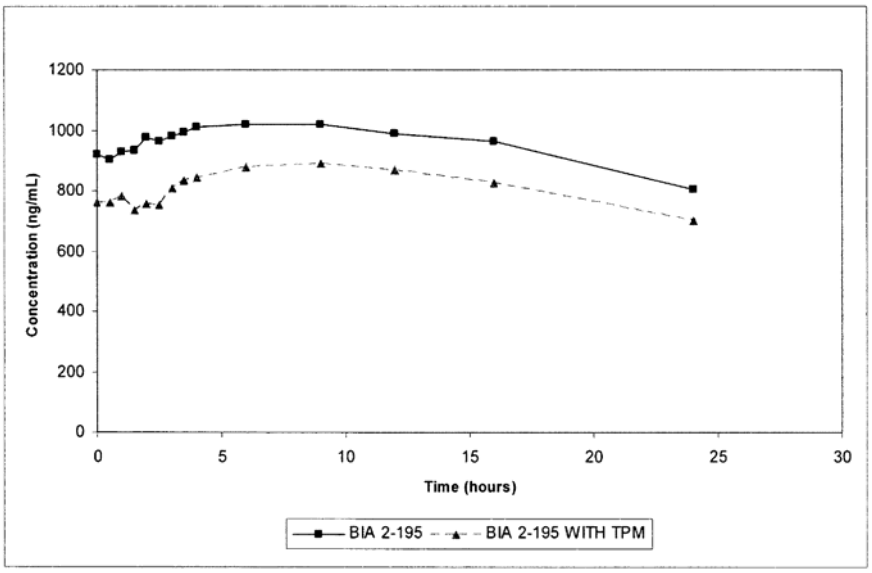
BIA 2-194 and BIA 2-195:

Plasma concentration of BIA 2-093 derived from the administration of the BIA 2-093 with Topiramate (Day 27) and BIA 2-093 alone (Day 8) was at BLQ. The mean measured plasma concentration versus time profile for BIA 2-194 ad BIA 2-195 are provided in the following figure.

Linear Profile of Mean BIA 2-194 Concentrations



Linear Profile of Mean BIA 2-195 Concentrations



The mean pharmacokinetic profiles indicate that co-administration of eslicarbazepine acetate (BIA 2-093) with topiramate results a decrease in eslicarbazepine (BIA 2-194) and BIA 2-195 concentrations.

A summary of the pharmacokinetic parameters for the metabolites eslicarbazepine (BIA 2-194) and BIA 2-195 and the statistical analysis are presented in the following tables.

Summary of Mean Pharmacokinetic Parameters for Eslicarbazepine (BIA 2-194)

PARAMETER	BIA 2-194 WITH TPM		BIA 2-194		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	9154.0	15.5	10066.2	13.7	24.20	<0.001
ln (C_{min}) (ng/mL)	9.1106	1.7	9.2083	1.5	25.27	<0.001
C_{max} (ng/mL)	21960.6	11.3	25414.8	14.7	13.06	<0.01
ln (C_{max}) (ng/mL)	9.9912	1.1	10.1328	1.5	13.63	<0.01
T_{max} (hours) §	2.00	48.1	2.00	48.7	0.69	N.S.
AUC_τ (ng·h/mL)	361733.9	10.7	389794.3	9.2	11.26	<0.01
ln (AUC_τ) (ng·h/mL)	12.7935	0.8	12.8693	0.7	12.40	<0.01
K_{el} ($hour^{-1}$)	0.0398	16.7	0.0358	21.3	11.81	<0.01
$T½_{el}$ (hours)	17.84	15.8	20.18	21.2	10.53	<0.01
Fluctuation (%)	85.26	13.6	94.11	14.4	3.34	<0.10
ln (Fluctuation) (%)	4.4379	2.9	4.5352	3.1	3.76	<0.10

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-194 with 90% CI

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-194 with TPM to BIA 2-194 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-194 WITH TPM	BIA 2-194		LOWER	UPPER
C_{min}	5.0	9050.7	9979.8	90.69	87.60	93.89
C_{max}	9.8	21832.5	25154.3	86.79	81.06	92.94
AUC_τ	5.5	359877.3	388219.4	92.70	89.21	96.32
Fluctuation	12.8	84.60	93.24	90.73	82.97	99.21

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

Summary of Pharmacokinetic Parameters for BIA 2-195

PARAMETER	BIA 2-195 WITH TPM		BIA 2-195		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	684.8	24.6	800.6	22.9	34.77	<0.001
ln (C_{min}) (ng/mL)	6.5012	3.8	6.6620	3.4	41.97	<0.001
C_{max} (ng/mL)	931.8	23.2	1062.6	22.1	13.71	<0.01
ln (C_{max}) (ng/mL)	6.8124	3.4	6.9465	3.1	13.55	<0.01
T_{max} (hours) §	9.00	46.5	6.00	65.2	3.93	<0.10
AUC_τ (ng·h/mL)	19611.8	24.0	22886.8	22.7	19.19	<0.001
ln (AUC_τ) (ng·h/mL)	9.8580	2.4	10.0159	2.2	19.15	<0.001
Fluctuation (%)	30.65	35.2	27.50	21.4	1.54	N.S.
ln (Fluctuation) (%)	3.3651	10.6	3.2894	7.3	0.92	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-195 with 90% CI

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-195 with TPM to BIA 2-195 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-195 WITH TPM	BIA 2-195		LOWER	UPPER
C_{min}	6.3	666.0	782.1	85.15	81.46	89.00
C_{max}	9.3	909.1	1039.5	87.45	81.95	93.32
AUC_τ	9.2	19110.9	22379.6	85.39	80.08	91.07
Fluctuation	20.4	28.94	26.83	107.87	93.70	124.18

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

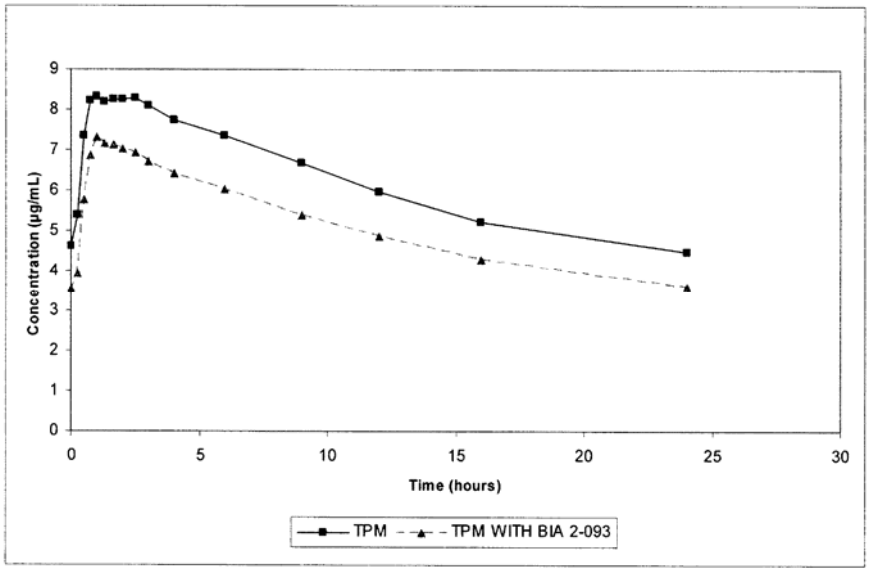
The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-194 with TPM to BIA 2-194 alone, are within the pre- specified 80% to 125% equivalence range.

The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-195 with TPM to BIA 2-195 alone, are within the pre- specified 80% to 125% bioequivalence range.

Topiramate

The mean measured plasma concentration versus time profile of Topiramate (TPM), derived from the administration of TPM alone and TPM with BIA 2-093, is depicted in the following figure.

Linear Profile of Mean Topiramate Concentration



There is an apparent decrease in mean concentrations of TPM when it was administered with BIA 2-093 relative to TPM alone.

The pharmacokinetic parameters of interest were submitted to statistical analysis are presented in the following tables.

Summary of Mean Topiramate Pharmacokinetic Parameters

PARAMETER	TPM WITH BIA 2-093		TPM		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (µg/mL)	3.507	13.8	4.449	8.3	129.52	<0.001
ln (C_{min}) (µg /mL)	1.2455	11.5	1.4893	5.7	94.23	<0.001
C_{max} (µg /mL)	7.725	11.0	9.488	12.6	44.22	<0.001
ln (C_{max}) (µg /mL)	2.0388	5.4	2.2424	5.7	48.92	<0.001
T_{max} (hours) §	1.00	38.2	0.88	63.4	0.07	N.S.
AUC_τ (µg ·h/mL)	121.028	10.5	147.703	9.0	203.14	<0.001
ln (AUC_τ) (µg ·h/mL)	4.7907	2.3	4.9914	1.8	182.36	<0.001
K_{el} ($hour^{-1}$)	0.0291	10.4	0.0288	9.5	0.11	N.S.
$T½_{el}$ (hours)	24.04	10.0	24.31	10.1	0.09	N.S.
Fluctuation (%)	83.92	10.6	82.21	23.9	0.11	N.S.
ln (Fluctuation) (%)	4.4245	2.4	4.3857	5.0	0.47	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Topiramate Pharmacokinetic Parameters

PARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		TPM with BIA 2-093 to TPM RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		TPM WITH BIA 2-093	TPM		LOWER	UPPER
C_{min}	6.7	3.475	4.434	78.36	74.95	81.93
C_{max}	7.7	7.681	9.416	81.58	77.48	85.89
AUC_{τ}	3.9	120.379	147.137	81.81	79.69	84.00
Fluctuation	15.1	83.47	80.29	103.96	94.03	114.94

* units are μg/mL for C_{min} and C_{max}, μg·h/mL for AUC_{τ} and % for Fluctuation.

The results demonstrate that the 90% confidence interval for Cmax geometric LSmeans of TPM with BIA 2-093 to TPM alone is not within the pre-specified 80 to 125% equivalence range. And the results also indicate that the 90% confidence interval for AUC, geometric LSmeans of TPM with BIA 2-093 to TPM alone, is not within the pre-specified 80 to 125% equivalence range. There is about a 19% decrease in mean Cmax and AUC when eslicarbazepine acetate is administered with Topiramate.

Pharmacokinetic Summary and Conclusions

The 90% confidence interval of the exponential of the ln-transformed Cmax and AUC, for BIA 2-194 with TPM versus BIA 2-194 alone were both within the bioequivalence acceptance range of 80 -125% for BIA 2-194 at steady-state.

The 90% confidence interval of the exponential of the ln-transformed Cmax and AUC for BIA 2- 1 95 with TPM versus BIA 2- 195 alone were both within the bioequivalence acceptance range of 80-125% for BIA 2-195 at steady-state.These results thus show that there was a no statistically significant impact of Topiramate on the pharmacokinetic properties of BIA 2-194 and BIA 2-195 when using a bioequivalence approach.

The 90% confidence interval of the exponential of the In-transformed Cmax and AUC, for TPM with BIA 2-093 versus TPM alone were both not within the bioequivalence acceptance range of 80-125% for TPM at steady-state. The results also show that there was a statistically significant impact of BIA 2-093 on the pharmacokinetic properties of TPM when using a bioequivalence approach.

The bioavailability of BIA 2-194 and BIA 2-195 at steady-state was equivalent to BIA 2-194 and BIA 2-195 in the presence of Topiramate. The bioavailability of topiramate at steady-state was not bioequivalent to topiramate in the presence of eslicarbazepine acetate. The confidence interval was outside the acceptance range of 80 to 125%.

Safety Summary

The sponsor reported that following the administration of eslicarbazepine acetate alone at 600 mg or 1200 mg, fifteen subjects (94%) reported adverse events. Fifteen subjects (94%) reported adverse events following the administration of topiramate alone at 100 or

200mg and twenty-nine subjects (97%) reported adverse events following the administration of eslicarbazepine acetate with topiramate.

The sponsor reported the following were summary of adverse events observed with subjects who took eslicarbazepine acetate alone. The events included abdominal pain upper, constipation, flatulence, lip dry, tongue coated, fatigue, injury, disturbance in attention, dizziness, dysarthia, headache, head discomfort, paraesthesia oral, somnolence, mood altered, pollakiuria, epistaxis, and viral upper respiratory tract infection were assessed to be possibly related to the study drugs.

The following adverse events were reported for those who took eslicarbazepine and topiramate. The events included palpitations, dry eye, ocular hyperaemia, abdominal distension, constipation, diarrhoea, flatulence, hypoaesthesia teeth, lip dry, reflux gastritis, fatigue, feeling drunk, feeling hot, hot flush, pyrexia, body temperature increased, decreased appetite, arthralgia, back pain, limb discomfort, musculoskeletal pain, muscular weakness, sensation of heaviness, coordination abnormal, disturbance in attention, dizziness, headache, paraesthesia, paraesthesia oral, somnolence, speech disorder, vision blurred, erection increased, euphoric mood, irritability, libido increased, mood altered, psychomotor retardation, dysuria, nasal congestion, pharyngolaryngeal pain, upper respiratory tract infection, dry skin, rash, rash maculo-papular, rash generalized, and pruritus.

The following were adverse events observed by those subjects who took topiramate alone. The events included dry eye, photophobia, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gingival bleeding, lip dry, nausea, oral pain, fatigue, injury, decreased appetite, back pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, disturbance in attention, dizziness, headache, insomnia, paraesthesia, paraesthesia oral, somnolence, vision blurred, depressed mood, euphoric mood, mood altered, urine abnormality, upper respiratory tract infection and toothache.

The sponsor reported that the maximal intensity reported for adverse events ranged from mild to severe. The events fatigue, somnolence, hot flush, constipation, euphoric mood, erection increased, upper respiratory tract infection, nausea, toothache, and decreased appetite were severe. Four (4) adverse events (rash generalized and upper respiratory tract infection) required the use of concomitant medication. The sponsor stated that an important part of these adverse events were secondary to the strong potential of topiramate to induce tiredness and somnolence, potential that was pushed further with the possible synergistic effect of eslicarbazepine acetate.
The sponsor reported that the observed average of number of adverse events per subject receiving eslicarbazepine acetate combined with topiramate in both groups A and B was similar to the sum of the average of number of adverse events per subject receiving eslicarbazepine acetate alone and receiving topiramate alone.

Reviewer comments: The reviewer agrees with the conclusions of the sponsor. Topiramate AUC and Cmax were significantly decreased by about 19% while no significant effect was observed on eslicarbazepine concentrations.

Study 121: A Phase 1, Open-Label Drug Interaction Study Between Eslicarbazepine Acetate 1200 mg and Phenytoin 300 mg Following Multiple Doses Administrations in Healthy Male Volunteers

Objectives: Primary: 1) To evaluate the effect of eslicarbazepine acetate (ESL) on the pharmacokinetics of Phenytoin (PHT) at steady-state. 2) To evaluate the effect of Penytoin (PHT) on the pharmacokinetics of eslicarbazepine acetate (ESL), BIA 2-194 and BIA 2-195 at steady-state.

Secondary: To assess the safety and tolerability of ESL and PHT when each drug was administered alone or in combination in healthy male volunteers following a multiple dose administration.

The study design is as follows.

Study Design	Single center, multiple doses, open-label, two parallel groups each receiving two formulations in a one sequence design
Study Population	Planned: 32 Group A: 15; Group B: 13 Age: 18 – 45 years (Mean ± SD:36 ± 6 years) Weight (Mean ±SD): 76.1 ± 9.5 kg
Treatment Groups + Dosage and Administration	Days 1 to 2 (Up-Titration) Group A: 600 mg once daily dose of ESL administered orally with 240 mL water in the morning for 2 consecutive days. Group B: 100 mg once daily dose of PHT administered with 240 mL of water in the morning for 2 consecutive days Days 3 to 8 Group A: 1200 mg (2x 600 mg tablets) once daily of ESL for 6 consecutive days Group B: 300 mg (3 x 100 mg capsules) once daily of PHT for 6-consecutive days Days 9 to 10 (Up-Titration) Group A: Concomitant doses of ESL 1200 mg and PHT 100 mg for 2 consecutive days Group B: Concomitant doses of ESL 1200 mg and PHT 300 mg for 2 consecutive days Days 11 to 27 Groups A + B: Concomitant doses of ESL 1200 mg and PHT 300 mg for 17 consecutive days At each dosing drug was administered with 240 mL of drug Eslicarbazepine Acetate 600 mg (BIA 2-093) Batch no. 050059-L Dilantin (Phenytoin) 100 mg, Batch no. 67160, 67183 and 67198 Diet: At least 10 hour overnight fast
Dosage and Admin.	Refer to Treatment groups
Sampling	PK of ESL (Group A)

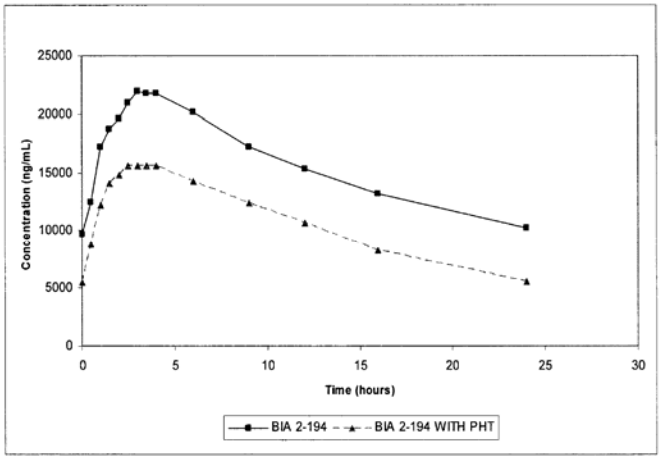
	Day 8: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration Day 27: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 16 and 24 hours after drug administration PK of PHT (Group B) Day 8: Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24 hours post dose Day 27: Pre-dose, 0.5,1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours post dose
Analysis	<u>ESL, BIA 2-194 and BIA 2-195</u> LC/MS/MS Assay range: ESL: 50 to 1000 ng/mL BIA 2-194 and BIA 2-195: 50 to 25000 ng/mL Precision: %CV≤ 15%; Accuracy: 94.9% - 107.2% <u>Phenytoin</u> HPLC with MS detection Assay Range: 50 – 10000 ng/mL QC: 50, 150, 2000 and 7500 ng/ml Precision: % CV < 4.5Accuracy: 95.4-104%
PK Assessment	Cmin, Cmax, AUCt, Tmax, Fluctuation, Kel and T ½ 2-sided 90% confidence interval (CI) of the geometric means (Day 27 to Day 8) for the Cmin, Cmax, AUCt.
Safety	Adverse events, physical examination, standard laboratory evaluation, 12-lead ECG, neurological function tests and neurological signs
PD Assessment	None

<u>Results</u>

<u>BIA 2-194 and BIA 2-195:</u>

Plasma concentrations of BIA 2-093 derived from the administration of the BIA 2-093 with PHT (Day 27) and BIA 2-093 alone (Day 8) were at BLQ. The mean measured plasma concentration versus time profiles of the metabolites BIA 2-194 and BIA 2-195, derived from the administration of BIA 2-093 with PHT and BIA 2-093 alone, are depicted in the following figures.

Linear Profile of Mean BIA 2-194 Concentrations



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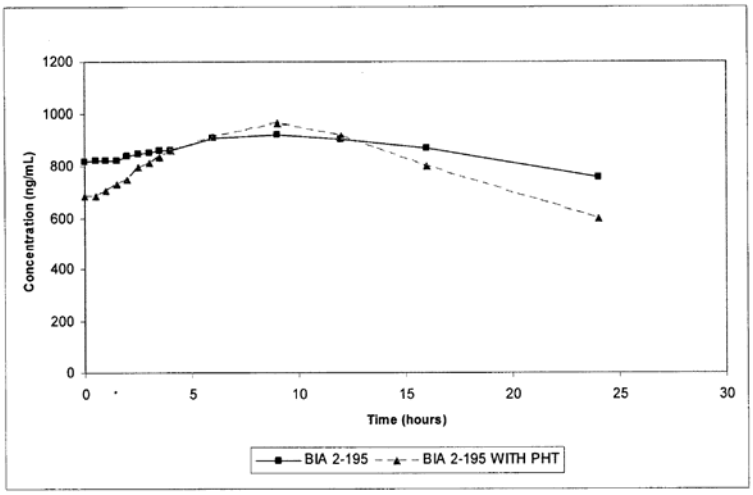
Linear Profile of Mean BIA 2-195 Concentrations



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The mean pharmacokinetic profiles indicate that co-administration of eslicarbazepine acetate (BIA 2-093) results in a decrease in the concentration of eslicarbazepine (BIA 2-194) and has no effect on the metabolite BIA 2-195.
A summary of the pharmacokinetic parameters for eslicarbazepine and the metabolite BIA 2-195 and the statistical analysis are presented in the following tables:

Summary of Mean Pharmacokinetic Parameters for Eslicarbazepine (BIA 2-194)

PARAMETER	BIA 2-194 WITH PHT		BIA 2-194		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	5316.5	23.0	9513.3	16.8	358.05	<0.001
ln (C_{min}) (ng/mL)	8.5524	2.8	9.1469	1.9	327.55	<0.001
C_{max} (ng/mL)	16350.6	12.6	23806.5	12.8	128.27	<0.001
ln (C_{max}) (ng/mL)	9.6943	1.3	10.0701	1.3	140.48	<0.001
T_{max} (hours) §	3.00	34.0	2.50	37.9	2.26	N.S.
AUC_τ (ng·h/mL)	251055.2	13.6	371574.9	11.7	263.20	<0.001
ln (AUC_τ) (ng·h/mL)	12.4247	1.1	12.8190	0.9	290.09	<0.001
K_{el} ($hour^{-1}$)	0.0547	15.8	0.0373	18.8	85.89	<0.001
$T½_{el}$ (hours)	12.98	16.2	19.16	17.2	69.29	<0.001
Fluctuation (%)	106.73	14.5	92.89	17.8	14.53	<0.01
ln (Fluctuation) (%)	4.6594	3.4	4.5164	4.0	13.52	<0.01

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-194 with 90% CI

RAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-194 with PHT to BIA 2-194 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-194 WITH PHT	BIA 2-194		LOWER	UPPER
C_{min}	9.0	5179.0	9385.1	55.18	52.08	58.47
C_{max}	8.7	16224.4	23625.9	68.67	64.94	72.62
AUC_τ	6.3	248862.5	369151.2	67.41	64.72	70.22
Fluctuation	10.7	105.58	91.50	115.38	107.74	123.57

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

Summary of Pharmacokinetic Parameters for BIA 2-195

PARAMETER	BIA 2-195 WITH PHT		BIA 2-195		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	594.8	24.9	739.1	24.2	29.74	<0.001
ln (C_{min}) (ng/mL)	6.3581	4.1	6.5765	3.8	41.45	<0.001
C_{max} (ng/mL)	976.9	19.9	954.3	19.9	0.46	N.S.
ln (C_{max}) (ng/mL)	6.8661	2.9	6.8422	2.9	0.57	N.S.
T_{max} (hours) §	9.00	16.5	9.00	44.8	1.40	N.S.
AUC_τ (ng·h/mL)	19471.2	20.9	20675.0	21.1	3.12	<0.10
ln (AUC_τ) (ng·h/mL)	9.8565	2.1	9.9157	2.2	3.85	<0.10
Fluctuation (%)	47.94	20.5	25.84	25.7	126.05	<0.001
ln (Fluctuation) (%)	3.8495	5.5	3.2254	7.2	138.34	<0.001

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Pharmacokinetic Parameters for BIA 2-195 with 90% CI

RAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		BIA 2-195 with PHT to BIA 2-195 RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		BIA 2-195 WITH PHT	BIA 2-195		LOWER	UPPER
C_{min}	9.3	577.1	718.0	80.38	75.72	85.33
C_{max}	8.7	959.2	936.6	102.41	96.87	108.26
AUC_τ	8.3	19082.6	20244.8	94.26	89.39	99.40
Fluctuation	14.6	46.97	25.16	186.67	170.01	204.96

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

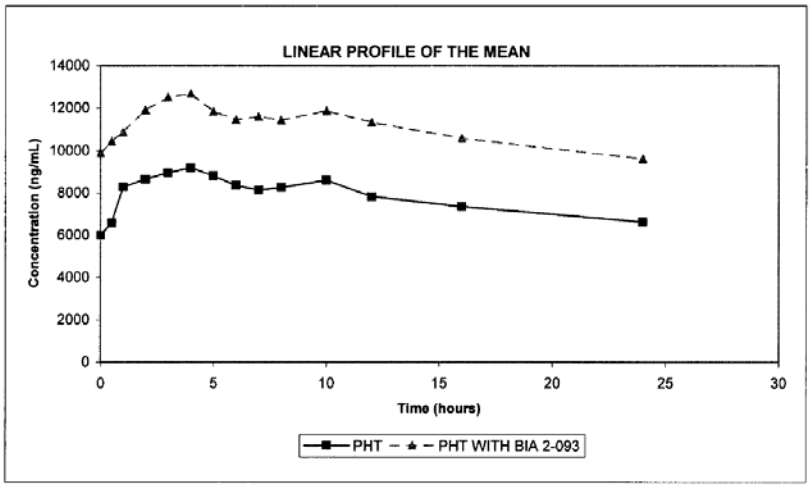
The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-194 with PHT to BIA 2-194 alone, are outside the pre- specified 80% to 125% equivalence range.

The results demonstrate that the 90% confidence interval for AUC and Cmax, geometric LSmeans of BIA 2-195 with PHT to BIA 2-195 alone, are within the pre- specified 80% to 125% bioequivalence range.

Phenytoin

The mean measured plasma concentration versus time profile of phenytoin (PHT), derived from the administration of PHT alone and PHT with BIA 2-093, is depicted in the following figure.

Linear Profile of Mean Phenytoin Concentration



The mean concentrations of PHT decreased when it was administered with BIA 2-093 relative to PHT alone.

The pharmacokinetic parameters of interest were submitted to statistical analysis and are presented in the following tables

Summary of Mean Phenytoin Pharmacokinetic Parameters

PARAMETER	PHT WITH BIA 2-093		PHT		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{min} (ng/mL)	9298.7	56.7	5969.1	47.5	17.32	<0.01
ln (C_{min}) (ng/mL)	8.9957	6.2	8.6121	4.7	29.35	<0.001
C_{max} (ng/mL)	12868.5	48.9	9405.1	38.5	13.28	<0.01
ln (C_{max}) (ng/mL)	9.3592	5.0	9.0912	3.8	18.47	<0.01
T_{max} (hours) §	4.00	48.9	4.00	58.8	0.14	N.S.
AUC_τ (ng·h/mL)	264784.8	52.0	186826.5	43.7	16.11	<0.01
ln (AUC_τ) (ng·h/mL)	12.3693	4.0	12.0682	3.1	23.40	<0.001
Fluctuation (%)	35.91	35.0	46.70	26.4	14.15	<0.01
ln (Fluctuation) (%)	3.5318	9.0	3.8112	7.0	16.53	<0.01

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation.

Statistical Comparison of Phenytoin Pharmacokinetic Parameters

ARAMETERS	INTRA-SUBJECT CV (%)	GEOMETRIC LS MEANS *		PHT with BIA 2-093 to PHT RATIOS (%)	90% CONFIDENCE LIMITS (%)	
		PHT WITH BIA 2-093	PHT		LOWER	UPPER
C_{min}	18.2	8068.5	5497.6	146.76	129.36	166.51
C_{max}	16.0	11605.2	8876.6	130.74	116.98	146.11
AUC_τ	16.0	235457.8	174235.1	135.14	120.95	151.00
Fluctuation	17.7	34.18	45.21	75.62	66.90	85.47

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ and % for Fluctuation.

The results demonstrate that the 90% confidence interval for Cmax geometric LSmeans of PHT with BIA 2-093 to PHT alone is outside the pre-specified 80 to 125% equivalence range. And the results also indicate that the 90% confidence interval for AUC, geometric LSmeans of PHT with BIA 2-093 to PHT alone, is outside the pre-specified 80 to 125% equivalence range.

Pharmacokinetic Summary and Conclusions

The major active metabolite of eslicarbazepine acetate responsible for its pharmacological activity is BIA 2-194. The bioavailability of BIA 2-194 at steady-state was not bioequivalent to BIA 2-194 in the presence of phenytoin. The addition of phenytoin as a concomitant therapy to eslicarbazepine acetate decreased AUC, and Cmax BIA 2-194 by about 30 to 35%. As phenytoin is a known enzymatic inducer, it may explain the decrease in AUC, of BIA 2-194. It has to be noted that the half-life of BIA 2-194 was also significantly decreased when combined with phenytoin. The bioavailability

of BIA 2-195 at steady-state was essentially bioequivalent to BIA 2-195 in the presence of phenytoin.

The bioavailability of phenytoin at steady-state was not bioequivalent to itself in the presence of eslicarbazepine acetate. The addition of eslicarbazepine acetate as a concomitant therapy with phenytoin increased AUC, and Cmax of phenytoin by about 30 to 35%.

Safety Summary

The sponsor stated that thirty (30) subjects participating in the trial reported adverse events throughout the course of this study. The events diarrhea and fatigue were severe. Seven (7) adverse events (headache, body temperature increased, toothache, tooth abscess, hypersensitivity, hypersensitivity syndrome and back pain) required the use of concomitant medication.

The sponsor reported that the observed average number of adverse events per subject receiving eslicarbazepine acetate combined with phenytoin (average of 7.4) was higher than the sum of the average number of adverse events per subject receiving eslicarbazepine acetate alone and receiving phenytoin alone (average of 5.6). Therefore, an increase in the number of adverse events per subject appears to be present when eslicarbazepine acetate was administered concomitantly with phenytoin.

Reviewer comments: The reviewer agrees with the conclusions of the sponsor. A pharmacokinetic interaction was observed when eslicarbazepine is co-administered with phenytoin. Patients should be closely monitored if these drugs are to be administered together.

PHARMACOMETRIC REVIEW

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions.

Is there any significant covariate which influences Eslicarbazepine PK?

The sponsor did not identify any significant covariate except for weight on CL/F. However, no race effect on CL/F can not be supported mainly due to the insufficient number of patients in Asian population in the observed dataset.

The sponsor conducted the population PK analysis to identify covariates and other AEDs which affects on the PK and exposure of eslicarbazepine. Three Phase III studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303) were included in the analysis. A 1-compartment model with first-order absorption and elimination was found to be an appropriate model to fit these data.

The final PK model identified neither gender nor race as significant covariates on eslicarbazepine CL/F or V/F. The renal function which was evaluated by Creatinine Clearance (CrCL) was not found to be significant factor on eslicarbazepine PK. The sponsor provided two potential reasons for that. One possibility is that the incorporation of the effect of weight on CL/F using the allometric function is serving as a surrogate for the effect of renal function as the Cockcroft and Gault-predicted CrCL values are correlated with weight. Another possibility is that the number of patients with CrCL values low enough to impact eslicarbazepine CL/F values observed in these studies was not large enough to detect a statistically significant effect on CL/F (7% of patients had CrCL values < 80 mL/min and 1% had CrCL < 50 mL/min).

The sponsor evaluated race effect as black .vs. non-black population where non-black population included Caucasian, Asian and Hispanic and the sponsor claimed that race did not influence on eslicarbazepine CL/F. However, the reviewer's analysis showed that there were too small number of Asian patients for comparisons with sufficient power and the sponsor's proposed labeling statement on race effect need to be modified accordingly.

Is there any co-administered antiepileptic drug (AED) which interacts with Eslicarbazepine PK?

Yes, the sponsor's population PK analysis in phase III studies in epileptic patients showed that three concomitant AEDs (carbamazepine, phenobarbital, and valproate) were found to affect the CL/F of eslicarbazepine. No influence of gabapentin, phenytoin, or levetiracetam on eslicarbazepine CL/F was detected on CL/F of eslicarbazepine. Also eslicarbazepine was shown to affect carbamazepine, phenytoin and levetiracetam CL/F.

Carbamazepine: The patients administered carbamazepine had a higher (10.5% - 31.6% at carbamazepine daily dosage of 200 mg BID to 400 mg TID) eslicarbazepine clearance compared to patients administered other AEDs. Also carbamazepine clearance was increased in proportion to the concomitant dose of eslicarbazepine; for carbamazepine 1000 mg daily and eslicarbazepine 400 mg, 800 mg, or 1200 mg daily, carbamazepine clearance increases 3.9%, 7.8%, and 11.8%, respectively.

Phenobarbital: Eslicarbazepine CL/F was expected to be higher (26%) in patients receiving concomitant phenobarbital (or other phenobarbital-like metabolic inducing agents), compared to patients receiving no other AEDs.

Phenytoin: Phenytoin CL/F was found to be decreased with increasing eslicarbazepine acetate dose by 3.6%, 7.1%, and 10.7% for eslicarbazepine acetate doses of 400 mg, 800 mg, 1200 mg daily, respectively, as compared to those not receiving concomitant eslicarbazepine acetate. No relevant effect of phenytoin on CL/F of eslicarbazepine was observed. However, the sponsor's population PK analysis clearly underestimates the effect compared to the results from the dedicated drug interaction study 2093-121.

Valporate: Eslicarbazepine CL/F was also found to be decreased in proportion to the concentration of concomitant valproate; eslicarbazepine CL/F is predicted to decrease by 8% - 22.6% over the valproate steady-state trough concentration range of 49.8 - 140 μg/mL. No clinically relevant effect of eslicarbazepine on the clearance of valproate was observed.

Levetiracetam: The patients administered eslicarbazepine had a higher (16.8%) levetiracetam clearance. No clinically relevant effect of levetiracetam on the clearance of eslicarbazepine was observed.

Gabapentine: There is no relevant pharmacokinetic interaction between eslicarbazepine and gabapentine based on the sponsor's population PK analysis.

The sponsor proposes to adjust dose for eslicarbazepine acetate when it is co-administered with carbamazepine, phenobarbital, (b) (4)

Is there any significant exposure-response relationship?

Yes, there is a significant relationship between the primary endpoint (standardized seizure frequency) and steady-state average eslicarbazepine concentration (Cav-ss), which was also confirmed by two secondary analyses; responder analysis by the sponsor and percent reduction in standardized seizure frequency from baseline relative to the maintenance phase by the reviewer.
The two phase III studies (BIA-2093-301, BIA-2093-302) were included in the exposure-response analyses. The doses of 400mg, 800mg and 1200mg were compared to placebo in both studies. Both studies failed to show statistically that 400mg group is significantly

better than placebo group in the efficacy analyses with respect to all endpoints including primary endpoint.
The sponsor performed exposure-response analysis using two endpoints (standardized seizure frequency and responder rate) as the response variables and a predicted steady-state average eslicarbazepine concentration as an exposure. The primary endpoint, seizure frequency, was defined as total standardized seizure frequency/28 days at maintenance phase. The values for this endpoint were log transformed prior to analysis. Since some patients reported no observed total standardized seizure frequency/28 days during the maintenance phase, the value of 4 was added to all seizure frequencies prior to log transformation.

The secondary endpoint, a responder was defined as a patient with at least 50% reduction in standardized seizure frequency from baseline relative to the maintenance phase (1 = responder, 0 = non-responder).
In addition to that, the reviewer evaluated the relationship using a different endpoint, relative change in seizure frequency from baseline, which is a typical primary endpoint for this indication.
The sponsor's analyses showed a significant relationship in both endpoints, which was also confirmed by the reviewer's independent analysis (see Figure 3, Figure 4 and Figure 9).

RECOMMENDATIONS

The Division of Pharmacometrics has reviewed the submission (NDA 22416) and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

LABEL STATEMENTS

The reviewer proposes to put following statements in the labeling.

12.3 Pharmacokinetics
Special Populations

Race

(b) (4)

No clinically significant effect of race (Caucasian n=534, Hispanic n=77, and Black n=12) on the pharmacokinetics of eslicarbazepine was noted in a population pharmacokinetic analysis of pooled data from the (b) (4) clinical trials

7. DRUG INTERACTIONS

Potential interactions between TRADENAME and other AEDs were assessed in clinical studies. The effect of these interactions are summarized in Table.

Table. Summary of AED interactions with TRADENAME.

AED	Dose of AED (mg/day)	TRADENAME Dose (mg/day)	Influence of TRADENAME on AED	Influece of AED on TRADENAME
Carbamazepine*	400-1200	400-1200	4-12% increase on CL/F	11-32% increase on CL/F
Phenobarbital*	150	1200	No influence	26% increase on CL/F
Phenytoin	300	1200	35% increase on AUC	33% decrease on AUC
Valproate*	250-2000	1200	No influence	8-26% decrease on CL/F
Lamotrigine	150	1200	12% decrease on AUC	4% decrease on AUC
Topiramate	200	1200	18% decrease on AUC	7% decrease on AUC
Levetiracetam*	750-4000	1200	No influence	No influence
Gabapentine*	800-3600	1200	No influence	No influence

* indicates the results based on population PK analysis

In a study in healthy subjects, concomitant administration of TRADENAME 1200 mg once daily and phenytoin 300 mg once daily resulted in an average decrease of 31-33% in exposure to eslicarbazepine, and an average increase of 31-35% in exposure to phenytoin. Based on these results, the dose of TRADENAME may need to be increased and the dose of phenytoin may need to be decreased.

Population pharmacokinetic analyses of Phase III studies in epileptic patients indicated that patients administered strong inducers of cytochrome P450 enzymes such as carbamazepine, phenobarbital had a higher eslicarbazepine clearance. A higher dose of TREADNAME may be necessary when administered concomitantly with higher doses of carbamazepine and phenobarbital.

(b) (4)

Pertinent regulatory background

This is the original submission. The sponsor is seeking the marketing approval for 400 mg, 600 mg, and 800 mg eslicarbazepine tablets indicated for the adjunctive therapy in the treatment of partial-onset seizures in adults.
Eslicarbazepine clinical program includes 22 Phase I studies in healthy subjects or special populations, 2 Phase II studies in adult and pediatric subjects with partial-onset seizures and 3 Phase III studies in adults with partial-onset seizures. In addition, 3 Phase II studies were performed in adults with bipolar disorder, an indication which is not the subject of this NDA. In total, eslicarbazepine was administered to 1667 subjects in 30 clinical studies. It is to note that the all efficacy and safety related clinical trials were conducted outside the U.S.
The recommended dose schedule is summarized as follows: Treatment should be initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at

increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily.

Results of Sponsor's Analysis

The sponsor submitted two separate reports; one is for a population PK analysis for drug-drug interaction study and the other is for a population PK and PK/PD analysis. They were listed in Table 1.

Table 1. Pharmcometrics related reports from the sponsor.

Document No	Reports
cog214016-20090716-aedpk.pdf	Pooled population PK analysis of AEDs after administration of eslicarbazepine acetate in patients with epilepsy: SCO/BIA-2093-301, (b) (4) BIA-2093-302 and (b) (4) BIA-2093- 303: drug-drug interaction population pharmacokinetic analyses
cog214016-20090716-eslpkpd1.pdf	Pooled population PK and PKPD analysis of eslicarbazepine acetate in patients with epilepsy: SCO/BIA-2093-301, (b) (4) BIA-2093-302 and (b) (4) BIA-2093-303.

Population PK analysis (cog214016-20090716-eslpkpd1.pdf)

The sponsor conducted the population PK analysis to identify covariates and other AEDs which affects on the PK and exposure of eslicarbazepine. Three Phase III studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303) were included in the analysis. The blood samples collected from patients in the 3 studies (Part I and Part II) were intended to be exclusively sparse samples, drawn before dosing on selected visits. Serial samples over 12 hours were collected from 50 patients in the extension (Part III) of the study BIA-2093-301.

The source data available from three Phase III studies included a total of 1602 sample records (629 patients).

A 1-compartment model with first-order absorption and elimination was found to be an appropriate model to fit these data. The eslicarbazepine concentration-time profile displays in Figure 1.

Figure 1. Eslicarbazepine concentration-time profile: percentiles of simulated data from the visual predictive check of the final pharmacokinetic model overlaid on the observed eslicarbazepine concentration data.

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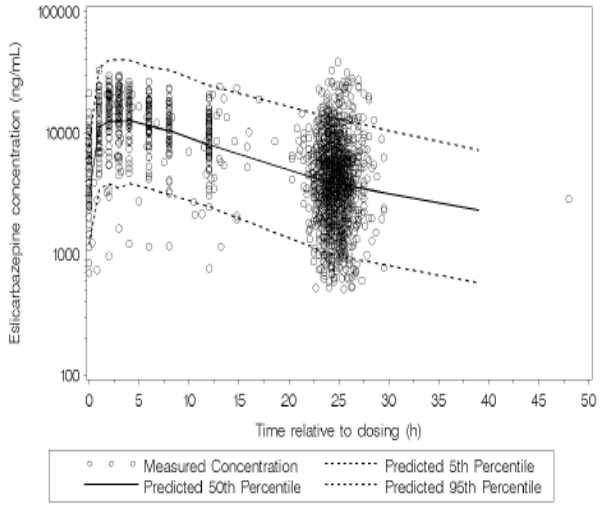

Source : sponsor's report, "Pooled population PK and PKPD analysis of eslicarbazepine acetate in patients with epilepsy: SCO/BIA-2093-301, (b) (4) BIA-2093-302 and (b) (4) BIA-2093-303" on page 116.

The final PK model identified neither gender nor race as significant covariates on eslicarbazepine CL/F or V/F. The renal function which was evaluated by Creatinine Clearance (CrCL) was not found to be significant factor on eslicarbazepine PK. The sponsor provided two potential reasons for that. One possibility is that the incorporation of the effect of weight on CL/F using the allometric function is serving as a surrogate for the effect of renal function as the Cockcroft and Gault-predicted CrCL values are correlated with weight. Another possibility is that the number of patients with CrCL values low enough to impact eslicarbazepine CL/F values observed in these studies was not large enough to detect a statistically significant effect on CL/F (7% of patients had CrCL values < 80 mL/min and 1% had CrCL < 50 mL/min).

As the most patients received 1 or more concomitant AEDs, the evaluation of the potential influence of these medications on eslicarbazepine CL/F was considered. Three concomitant AEDs (carbamazepine, phenobarbital, and valproate) were found to statistically significant on CL/F of eslicarbazepine. No influence of gabapentin, phenytoin, or levetiracetam on eslicarbazepine CL/F was detected.

Compared to patients receiving no concomitant AEDs, those receiving carbamazepine were predicted to have a higher eslicarbazepine CL/F (10.5% - 31.6% for carbamazepine doses ranging from 200 mg twice daily to 400 mg three times daily).

Eslicarbazepine CL/F was expected to be higher (26%) in patients receiving concomitant phenobarbital (or other phenobarbital-like metabolic inducing agents), compared to patients administered no other AEDs.

Eslicarbazepine CL/F was also found to be decreased in proportion to the concentration of concomitant valproate; eslicarbazepine CL/F is predicted to decrease by 8% - 22.6% over the valproate steady-state trough concentration range of 49.8 - 140 μg/mL.
The equation for a typical CL/F of eslicarbazepine from the final model is presented below:

$$CL/F_j = \left[3.88 + 0.818 \times \frac{dose_{carbamazepine_j}}{800} - 0.312 \times \frac{Cp_{valproate_j}}{48.8} + 1.01 \times flag_{phenobarbital\text{-}like_j}\right] \times \left(\frac{wt_j}{69}\right)^{0.75}$$

Where:

$dose_{carbamazepine_j}$ = the daily dose of carbamazepine in the *j*th patient

$Cp_{valproate_j}$ = the pre-dose (steady-state) valproate concentration in the *j*th patient

$flag_{phenobarbital\text{-}like_j}$ = flag variable for the presence of phenobarbital or phenobarbital-like metabolic inducers in the *j*th patient (0 or 1)

wt_j = weight in the *j*th patient

The sponsor proposed higher dose of eslicarbazepine acetate when co-administered with higher doses of carbamazepine and with concomitant administration of phenobarbital (or other phenobarbital-like metabolic inducing agents) but no dose adjustment for valproate.

Please refer to appendix for the details on population PK analysis.

Exposure-Response analysis (cog214016-20090716-eslpkpd1.pdf)

The two phase III studies (BIA-2093-301, BIA-2093-302) were included in the sponsor's exposure-response analyses. A total of 1256 observations (628 patients) were included in the PK/PD dataset. The doses of 400mg, 800mg and 1200mg with placebo were explored and Table 2 summarizes the study design.

Table 2. Overview of Primary Study Design Features for the Pivotal Phase III Studies 2093-301 and 2093-302

Study	8-week Baseline Period	Randomized Treatment Group (mg)	Titration Dose (mg), Week 1/Week 2	Maintenance Dose (mg), Weeks 1-12	Tapering-off Dose (mg), Week 1/Week 2/Weeks 3-4
2093-301	Single-blind Placebo	400	400/400	400	400/400/Placebo
		800	400/800	800	800/400/Placebo
		1200	400/800	1200	800/400/Placebo
		Placebo	Placebo/placebo	Placebo	Placebo/placebo/placebo
2093-302	Observational	400	400/400	400	Not applicable
		800	800/800	800	Not applicable
		1200	800/800	1200	Not applicable
		Placebo	Placebo/placebo	Placebo	Not applicable

Two endpoints were evaluated for exposure- response analyses for efficacy — seizure frequency (primary endpoint), responder rate.
The primary endpoint, seizure frequency was defined as total standardized seizure frequency/28 days at maintenance phase. The values for this endpoint were log transformed prior to analysis. Since some patients reported no observed total standardized seizure frequency/28 days during the maintenance phase, the value of 4 was added to all seizure frequencies prior to log transformation. Patients included in the exposure-response analyses dataset had at least one reported seizure frequency/28 days (at baseline or during the maintenance phase).

The secondary endpoint, a responder was defined as a patient with at least a 50% reduction in standardized seizure frequency from baseline relative to the maintenance phase (1 = responder, 0 = non-responder).
The predicted steady-state average eslicarbazepine concentration (Cavss) was used for an exposure. As shown in Figure 2, it appears to be proportional to dose.

Figure 2. The distribution of Cavss by dose group.

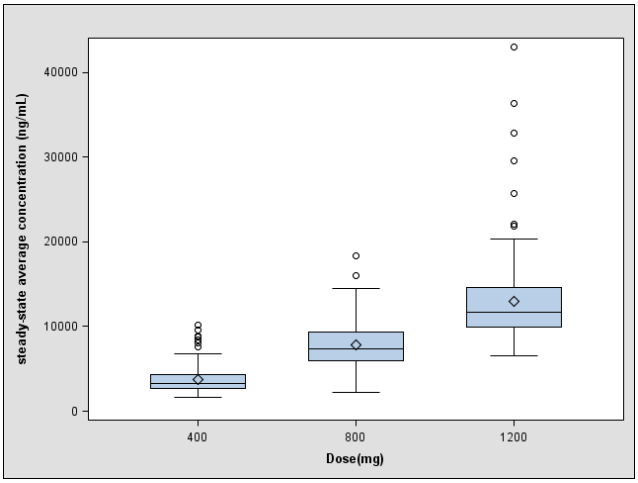

Table 3 summarizes the seizure frequency at baseline and during the maintenance phase by study and also dose group. At baseline, the overall median standardized seizure frequency was 7.6 with large variability (range :2.0 to 153.5), which was reduced by taking log-transformation. The baseline median seizure frequency was similar in both studies but slightly lower in the placebo group compared to all active groups.

Table 3. Summary statistics of standardized seizure frequency at baseline and during the maintenance phase, by Study (top) and dose group (bottom).

Patient Characteristic		Study SCO/BIA-2093-301	Study PRA/BIA-2093-302	Overall
Baseline ln (standardized seizures + 4)	Mean (SD)	2.596 (0.538)	2.686 (0.571)	2.640 (0.556)
	Median	2.410	2.514	2.448
	Minimum, Maximum	1.79, 5.06	1.79, 4.52	1.79, 5.06
	n	322	306	628
Baseline standardized seizures	Mean (SD)	12.245 (15.289)	13.761 (13.506)	12.984 (14.456)
	Median	7.132	8.351	7.566
	Minimum, Maximum	2.00, 153.48	2.00, 87.93	2.00, 153.48
	n	322	306	628
Maintenance ln (standardized seizures + 4)	Mean (SD)	2.596 (0.538)	2.686 (0.571)	2.640 (0.556)
	Median	2.410	2.514	2.448
	Minimum, Maximum	1.79, 5.06	1.79, 4.52	1.79, 5.06
	n	322	306	628
Maintenance standardized seizures	Mean (SD)	9.226 (14.146)	11.627 (14.580)	10.402 (14.399)
	Median	5.600	6.421	5.950
	Minimum, Maximum	0.00, 141.01	0.00, 144.31	0.00, 144.31
	n	319	306	625

Abbreviations: ln, natural log; SD, standard deviation.

Patient Characteristic		Placebo	400 mg	800 mg	1200 mg	Overall
Baseline ln (standardized seizures + 4)	Mean (SD)	2.607 (0.554)	2.644 (0.508)	2.666 (0.586)	2.655 (0.578)	2.640 (0.556)
	Median	2.387	2.491	2.431	2.497	2.448
	Minimum, Maximum	1.79, 5.06	1.87, 4.09	1.95, 4.42	1.79, 4.98	1.79, 5.06
	n	201	148	152	127	628
Baseline standardized seizures	Mean (SD)	12.592 (15.697)	12.288 (10.364)	13.650 (14.069)	13.618 (16.867)	12.984 (14.456)
	Median	6.877	8.073	7.368	8.145	7.566
	Minimum, Maximum	2.00, 153.48	2.50, 55.50	3.00, 78.69	2.00, 141.53	2.00, 153.48
	n	201	148	152	127	628
Maintenance ln (standardized seizures + 4)	Mean (SD)	2.512 (0.653)	2.431 (0.562)	2.373 (0.645)	2.322 (0.660)	2.420 (0.635)
	Median	2.394	2.296	2.222	2.159	2.298
	Minimum, Maximum	1.39, 4.84	1.39, 4.08	1.39, 5.00	1.39, 4.98	1.39, 5.00
	n	198	148	152	127	625
Maintenance standardized seizures	Mean (SD)	12.016 (16.165)	9.622 (9.998)	9.924 (15.018)	9.365 (15.004)	10.402 (14.399)
	Median	6.959	5.929	5.228	4.667	5.950
	Minimum, Maximum	0.00, 122.33	0.00, 55.34	0.00, 144.31	0.00, 141.01	0.00, 144.31
	n	198	148	152	127	625

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Seizure Frequency Model

The log-transformed seizure frequency was best described by an Emax model including the sum of a baseline, a constant placebo effect, and the eslicarbazepine drug effect as significant covariates as follows;

$$\ln(\text{std seiz freq}+4)_j = 2.64 - 0.0971 \times plac_j + (1 - plac_j) \times \left[\frac{-0.337 \times \left(\frac{\ln(bseiz_j)}{2.45} \right) \times C_{av-ss_j}}{1970 + C_{av-ss_j}} \right]$$

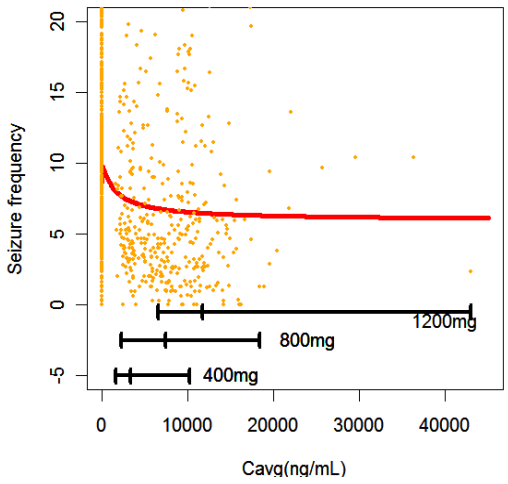
Where:

$plac_j$	=	an indicator variable for treatment with placebo (1 = yes, 0 = no) in the jth patient
C_{av-ss_j}	=	steady-state average eslicarbazepine concentration in the jth patient
$\ln(bseiz_j)$	=	natural log of the baseline standardized seizure frequency in the jth patient

The maximum predicted drug effect was found to be related to the baseline seizure frequency; a larger maximum effect is expected with higher baseline seizure frequencies. EC50 was estimated as eslicarbazepine $C_{av\text{-}ss}$ of 1970 ng/mL, which is less than the median value associated with the lowest dose of 400 mg.

Figure 3 presents the relationship between seizure frequency and eslicarbazepine Cavss. The sponsor's model predicts seizure frequencies of 8.7, 7.3, 6.7 and 6.6 at placebo, eslicarbazepine acetate daily doses of 400 mg (median Cavg: 3336 ng/mL), 800 mg (median Cavg: 7341 ng/mL), and 1200 mg (median Cavg: 11664 ng/mL), respectively, which compared to the observed median frequencies of 7.0, 5.9, 5.2 and 4.7. Neither weight nor sex was found to be statistically significantly related to seizure frequency model parameters.

Figure 3. The relationship between standardized seizure frequency and Cavss. The orange dots represent observed data and red solid line indicates the model predicted relationship. Each horizontal line is the range of exposure (Cavss) at each dose group.



Model for Probability of Response

The probability of response (defined as at least a 50% reduction in standardized seizure frequency/28 days from baseline to maintenance) was modeled using a logistic regression model which included the sum of a constant placebo effect and the predicted eslicarbazepine Cavss as follows;

$$Logit_j = -1.46 \times plac_j + (1 - plac_j) \times \left[-1.09 + 0.000051 \times C_{av-ss_j}\right]$$

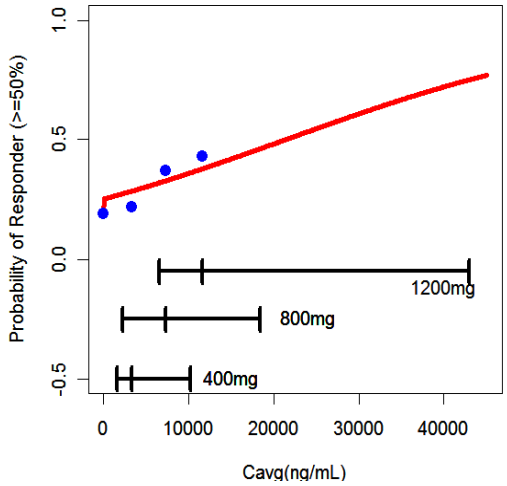
Where:

$plac_j$ = an indicator variable for treatment with placebo (1 = yes, 0 = no) in the jth patient

C_{av-ss_j} = steady-state average eslicarbazepine concentration in the jth patient

As shown in Figure 4, there appears to be significant relationship between eslicarbazepine Cavss and the probability of responder. The sponsor's logistic model predicts a probability of response of 0.19 for patients receiving placebo, which is consistent with observed proportion of 0.19. The model-predicted probability of response for patients taking eslicarbazepine acetate were 0.28, 0.33, and 0.38 for 400 mg, 800 mg, and 1200 mg of eslicarbazepine acetate, respectively, which appears to be similar to the observed proportions of 0.22, 0.37 and 0.43.
There was no additional covariate which was found to influence the probability of response.

Figure 4. Probability of responder .vs.eslicarbazepine Cavss. The blue dots represent the observed probability at each quartile of eslicarbazepine Cavss and the red solid line is the model-predicted probability of responder. Each black horizontal bar indicates the range of Cavss at each dose group.



Drug-Drug Interaction study (cog214016-20090716-aedpk.pdf)

In this analysis the sponsor aimed to investigate the effect of eslicarbazepine acetate on the pharmacokinetics (PK) and exposure of 6 co-administered antiepileptic drugs (AEDs) (carbamazepine, gabapentin, levetiracetam, phenobarbital, phenytoin, and valproate) after accounting for the effects of other potential factors that may influence PK variability. The three Phase III studies (BIA-2093-301, BIA-2093-302 and BIA-2093-303) were included, and blood samples were intended to be exclusively sparse samples, drawn before dosing on selected visits. The schedule for blood sample is summarized below;

BIA-2093-302

		Double-Blind (Part I)					1-Year Open-Label Extension (Part II)					
Visit	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Disc
Weeks/months	-8 Weeks	Day 1	2 Weeks	4 Weeks	8 Weeks	14 Weeks	+1 Month	+3 Months	+6 Months	+9 Months	+12 Months	
Blood sampling for AED concentrations		X				X	X		X		X	X

BIA-2093-301/303

		Double-Blind (Part I)						1-Year Open-Label Extension (Part II)					
Visit	Visit 1	Visit 2	Visit 3	TC	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Disc
Weeks/months	-8 Weeks	Day 1	2 Weeks	4 Weeks	8 Weeks	14 Weeks	18 Weeks	+1 Month	+3 Months	+6 Months	+9 Months	+12 Months	
Blood sampling for AED concentrations		X				X	X	X		X		X	X

Abbreviations: AED, antiepileptic drug; Disc, upon early termination; TC, telephone contact during the 12-week maintenance period.

The sponsor developed population PK models separately for each 6 AED (carbamazepine, gabapentin, levetiracetam, phenobarbital, phenytoin, and valproate) because of the nature of sparse sampling; the model estimated only 1 parameter, the apparent oral clearance (CL/F), which is used to predict steady-state average concentrations (Cavss) as follows,

$$C_{av-ss} = \frac{R_0}{CL/F}$$

Where:

C_{av-ss} = AED steady-state average concentration

R_0 = dosing rate (mg/h); that is, total daily dose divided by 24

CL/F = apparent oral clearance (L/h)

The results from population PK analysis for drug-drug interaction are summarized below.

- Carbamazepine : CL/F was increased with increasing eslicarbazepine acetate dose, carbamazepine dose, phenobarbital dose, and ALT, as well as decreasing ALP. For patients not receiving concomitant phenobarbital, and having the population median values of ALT and ALP (17 U/L and 81 U/L, respectively), carbamazepine CL/F is expected to increase 3.9%, 7.9%, and 11.8% with the combination of 1000 mg carbamazepine daily and 400 mg, 800 mg, or 1200 mg eslicarbazepine acetate daily, respectively.

- Phenytoin : CL/F was found to be decreased with increasing eslicarbazepine acetate dose by 3.6%, 7.1%, and 10.7% for eslicarbazepine acetate doses of 400 mg, 800 mg, 1200 mg daily, respectively, as compared to those not receiving concomitant eslicarbazepine acetate.

- Gabapentin : CL/F is related to CrCL in a linear manner, however, concomitant administration of carbamazepine or valproate and body weight were not found to be statistically significant predictors of gabapentin CL/F.

- Levetiracetam : CL/F was 16.8% higher in patients with the population median value of CrCL (109.2 mL/min) who were co-administered eslicarbazepine acetate, regardless of dose, as compared to those not receiving eslicarbazepine acetate. Creatinine clearance was also found to be a statistically significant predictor of levetiracetam CL/F.

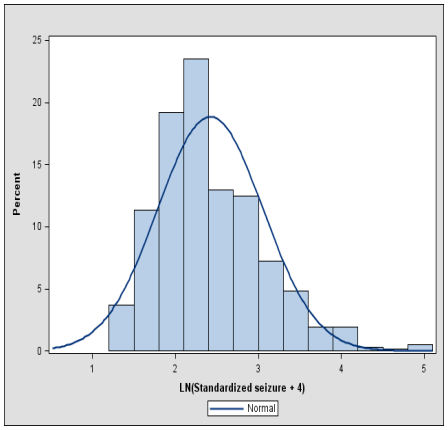
- Valproate : CL/F appears to be increasing with the doses of both carbamazepine and valproate. Dose adjustment of valproate may be necessary with concomitant administration of carbamazepine.

- Phenobarbital: only significant factor on CL/F was the administered dose of Phenobarbital.

Reviewer's comment:

- *No race effect on eslicarbazepine PK could be due to either lack of power or by combining three different races into one category. Therefore, race effect need to be re-evaluated with more appropriate methods.*

- *The sponsor's population PK analysis on drug interaction between Eslicarbazepine and Phenytoin clearly underestimates the effect compared to the result from the dedicated drug-drug interaction sudy (study 2093-121). It could be due to different populations in the two analyses; one for healthy subjects, the other for patients.*
- *In the exposure-response analysis, the sponsor needs to provide the justification of adding 4 to the seizure frequency as the density plot below clearly shows violation of normal distribution.*



Reviewer's Analysis

Introduction

In the sponsor's population PK analysis, the sponsor evaluated the race effect by black .vs. non-black where non-black included Caucasian, Asian and Hispanic patients and proposed to put the statement of no significant race effect on PK of eslicarbazepine in the label. However, no rationale was provided for combining Caucasian, Asian and Hispanic patients into one category. In the reviewer's analysis, the race effect was evaluated based on pairwise comparison among all races.
Also, the sponsor re-submitted the dataset for efficacy analysis after having corrected the errors in seizure calculation. The reviewer has re-run exposure-response analyses and compared the results.
Lastly, the sponsor evaluates the exposure-response relationship using two enpdoints – standardized seizure frequency over 4 weeks (primary endpoint) and responder rate (one of secondary endpoint in efficacy analysis). The reviewer conducted an independent exposure-response analysis using the relative reduction in standardized seizure frequency during maintenance phase from baseline as an endpoint. This endpoint is routinely used in regulatory decision for the same indication.

Objectives

- To re-evaluate the race effect on eslicarbazepine PK

- To compare the results before and after correction in the seizure calculation.
- To confirm the significant exposure-response relationship by independent analysis using a different endpoint.

Methods

Race effect on PK

The reviewer evaluated the power of the PK dataset to identify race effect based on simulation with the following assumptions: 1) 30% difference in CL between any two races will be considered significant. 2) Nominal type I error rate of 0.05 is used for each comparison 3) 43% between subject variability for CL from the final model 4) Shrinkage due to empirical Bayesian estimation of individual CL is ignorable as (1-0.31/0.43) =0.28.

Re-run of the sponsor's Exposure-Response analysis using new dataset

New dataset for exposure-response analyses was built and the same models as those in the previous analyses were fitted for both endpoints using NONMEM. The results including parameter estimates and standard errors were compared.

Exposure-Response analysis using percent change in standardized seizure frequency from the baseline

The relative change in standardized seizure frequency from baseline was log-transformed after adding 1.6 to ensure a normality assumption (see Figure 5) as follows;

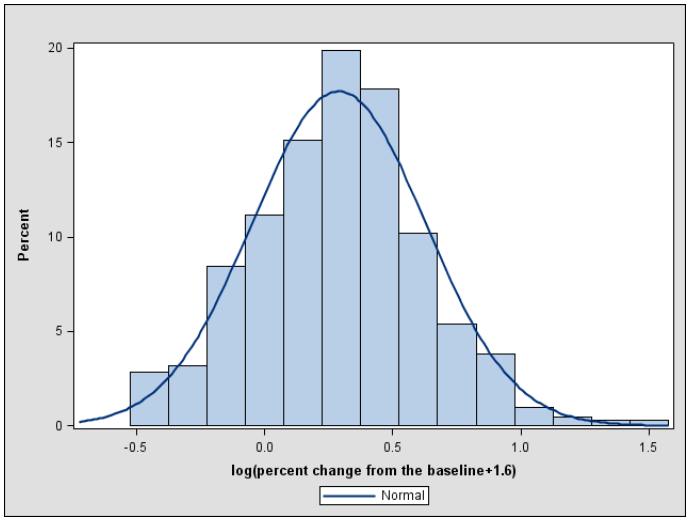
$$Y = \log(\frac{S_m - S_b}{S_b} + 1.6)$$

where

S_m : standardized seizure frequency during maintenance period

S_b : standardized seizure frequency at baseline

Figure 5. The distribution of log-transformed percent seizure reduction from baseline.



Based on an exploratory graphical analysis, Emax model was fitted to the data and gnls function in S-plus 7.0 was employed for a nonlinear regression using generalized least square method.

$$Y_i = E_o + \frac{E\max \times Cavss_i}{EC_{50} + Cavss_i} + \varepsilon_i$$

where

C_{avss} : steady-state average eslicarbazepine concentration for subject i

E_0 : placebo effect

E_{max} : maximum effect associated with C_{avss}

EC_{50} : C_{avss} leading to 50% of maximum change in the response variable

$\varepsilon_i \sim N(0, \sigma^2)$

Data Sets

Data sets used are summarized in Table 4.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
BIA-2093-301, BIA-2093-302	Eff3012.csv	

Software

SAS 9.2 and S-plus 7.0 are used for the analysis.

Results

Race effect on PK

Table 5 presents the distribution of race which was included for population PK analysis which shows a very limited sample sizes for Asian population.

Table 5. The distribution of Race in population PK analysis dataset.

Race/Ethnicity	BIA 2093-301 (N=311)	BIA 2093-302 (N=207)	BIA 2093-303 (N=111)	Overall (N=629)
Caucasian	311	183	40	534
Black	0	12	0	12
Asian	0	5	1	6
Hispanic	0	7	70	77

Table summarizes the results from the simulation for power evaluation; the lack of power was detected for comparisons involving Asians due to the small sample size (N=6).
Hence, the sponsor's claim of no significant race effect should be modified.

Table 6. The results from power calculation

Race comparison	Power
Caucasian .vs. Black	0.80
Caucasian .vs. Asian	0.52
Caucasian .vs. Hispanic	1
Black .vs. Asian	0.34
Black .vs. Hispanic	0.77
Asian .vs. Hispanic	0.45

The re-run of the sponsor's Exposure-Response analysis using new dataset

Table 6 and Table 7 summarized the results from re-run of final model for primary endpoint (log (seizure frequency)) and responder analysis. There is little difference shown in both endpoints, which is consistent with the primary efficacy analysis results.

Table 6. The comparison of Parameter estimates for seizure frequency from the final model between old and new (corrected) datasets

Parameter	Final parameter Estimate				Between subject variability			
	OLD		NEW		OLD		NEW	
	Mean	% SEM	Mean	% SEM	Final estimate	%SEM	Final estimate	%SEM

					(%CV)		(%CV)	
Baseline standardized seizure	2.64	0.8	2.65	0.8	54	7.7	54	7.6
Constant placebo effect	-0.097	29.8	-0.105	26.7	38	18.1	36	18.2
Emax at the median baseline seizure	-0.337	12.3	-0.322	12.1	123	18.8	125	18.5
EC50 (ng/mL)	1970	43.6	2070	41.8	—	—	—	—
Additive RV	10%	66.6	10.9%	52.1	—	—	—	—
objective function	-712.517		-739.167		—	—	—	—

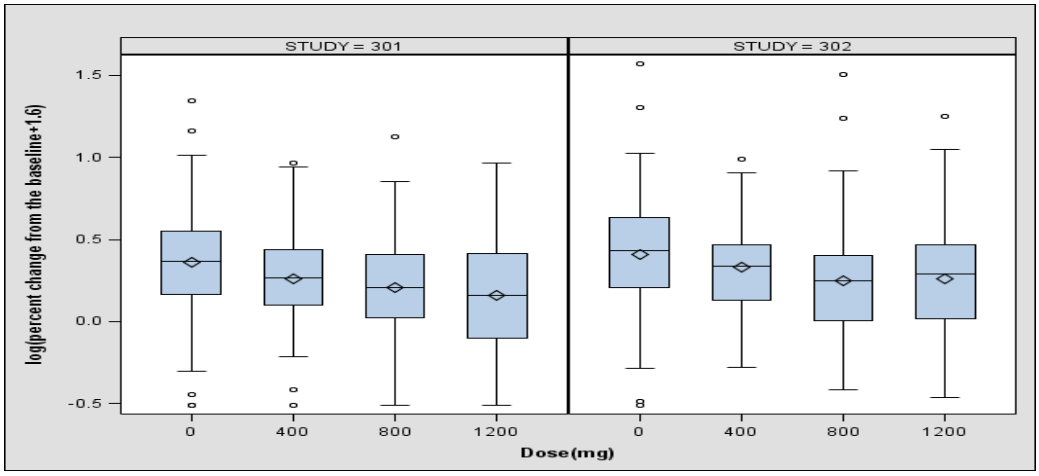
Table 7. Parameter estimates for responder analysis comparing old and new (corrected) datasets

	Final Parameter Estimate			
	OLD		NEW	
Parameter	Mean	%SEM	Mean	%SEM
Placebo effect	-1.46	12.3	-1.46	12.3
Intercept	-1.09	18.1	-1.06	18.5
slope	0.000051	40.2	0.0000427	47.5
Objective function	-734.353		730.695	

The reviewer's Exposure-Response analysis using percent change in standardized seizure frequency from the baseline

First, dose-response relationship was explored using PK/PD dataset (Figure 6). There appears to be more reduction in seizure frequency as a dose increases in both studies. The median percent reduction from the baseline with pooled data were 13.2% for placebo and 22.7%, 33.3% and 32.6% at doses of 400mg, 800mg and 1200mg, respectively.

Figure 6. The relative change in standardized seizure frequency from baseline (log scale) by dose group and study



Next, a steady-state average eslicarbazepine concentration was binned according to a quartile to see the observed exposure-response relationship before the model was fitted. Figure 7 displays the distribution of Cavss.

Figure 7. The distribution of steady-state average concentration at each dose by study.

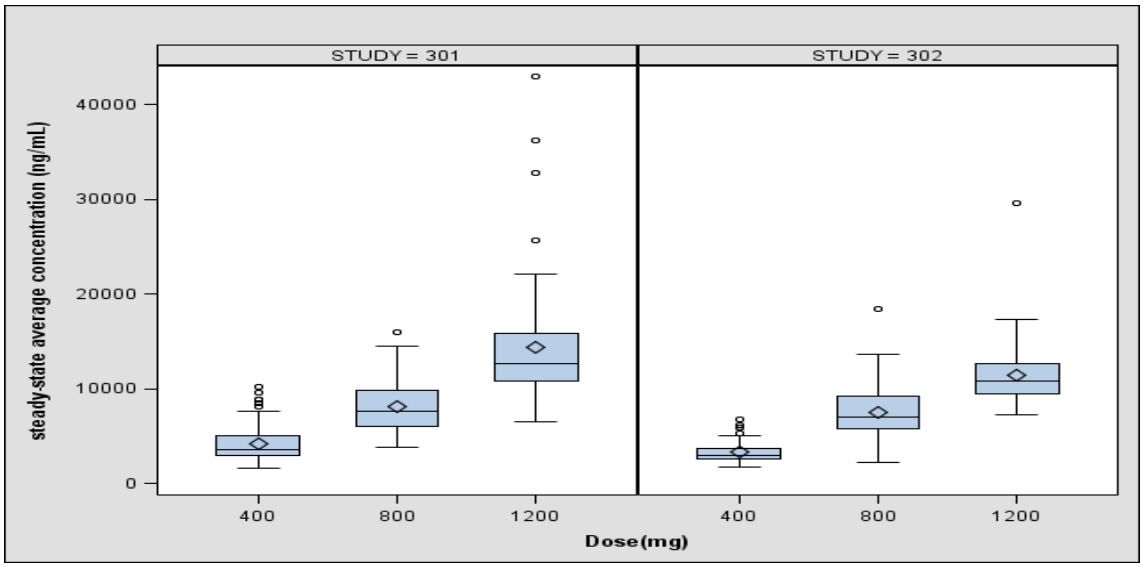
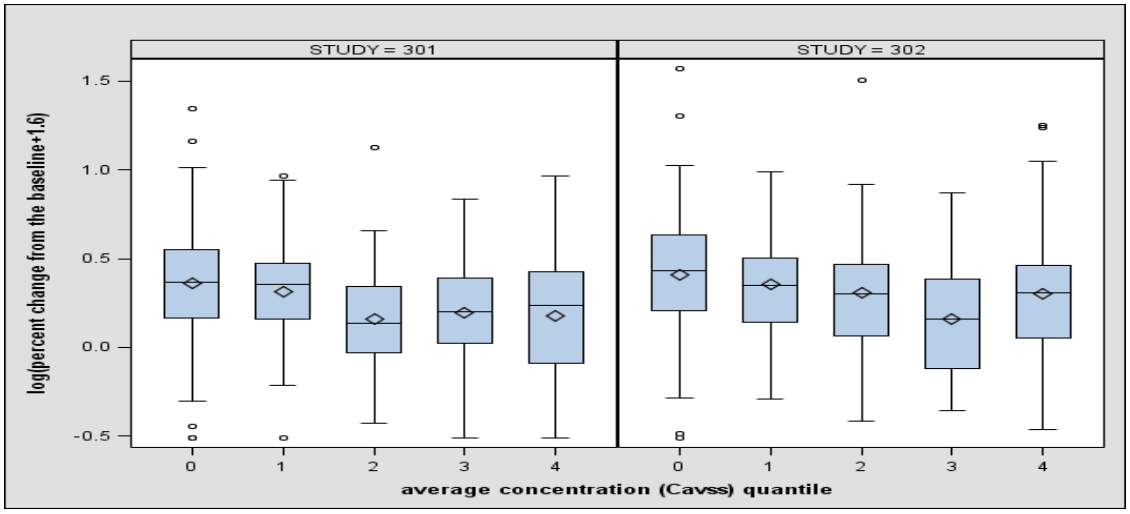


Figure 8 shows the observed relative change in seizure frequency from baseline as a log-scale at each quartile of Cavss by study. In both studies, it shows significant reduction in seizure frequency with higher exposure and it seems to reach a plateau at the 3rd quartile which is about 7000 ng/mL for both studies.

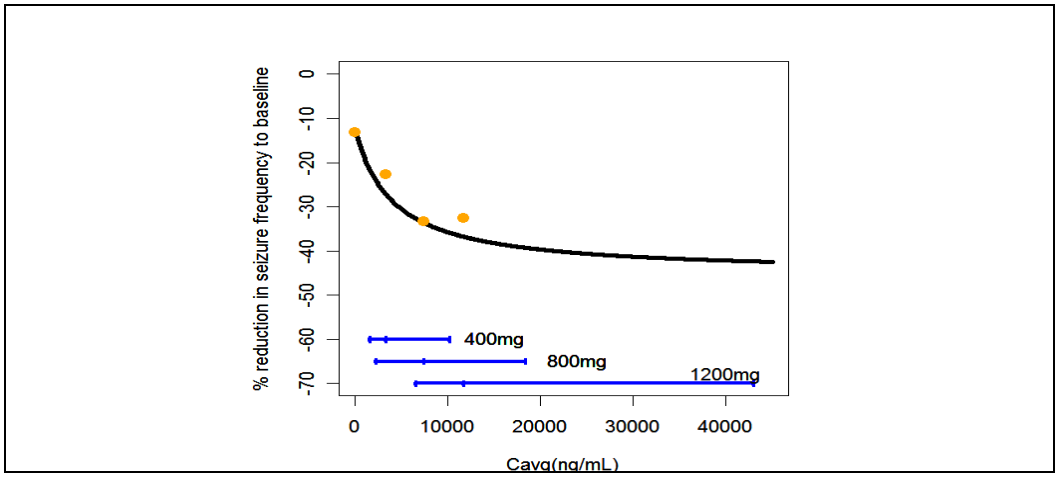
Figure 8. The relative change in standardized seizure frequency from baseline (log scale) at each quartile of Cavss and study.



The reviewer pooled the data from two studies as there was not much difference observed between two studies in the relationship of relative change and Cavss. According to the reviewer's model, EC50 was estimated as 4544 ng/mL which is higher than the median Cavss at the dose of 400mg (3336 ng/mL) while the sponsor's EC50 for seizure frequency model was 2070 ng/mL.

Figure 9 shows the model-predicted relationship with observed data at the median of Cavss at each dose group; it is apparent that there is a significant relationship between exposure and relative change in seizure frequency from baseline. When it was converted to original scale, multiplied by 100, the reviewer's model predicts percent reduction of 12.4%, 27.2%, 33.6% and 36.8% at placebo, eslicarbazepine acetate daily doses of 400 mg (median Cavg: 3336 ng/mL), 800 mg (median Cavg: 7341 ng/mL), and 1200 mg (median Cavg: 11664 ng/mL), respectively, as compared to the observed median reduction of 13.2%, 22.7%, 33.3% and 32.6%.

Figure 9. Model-predicted relationship between relative change (%) in seizure frequency and steady-state average concentration. The orange dots indicate the observed median percent reduction at the median Cavss of each dose group and the black solid line represents model-predicted relationship. Each horizontal line is the range of exposure (Cavss) at each dose group.



In conclusion, the reviewer's independent analysis for relative seizure frequency change is consistent with the sponsor's findings based on seizure frequency and responder endpoints.

Listing of Analyses Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Pchg.emax.ssc Reviewer's analysis.sas	The model fit Exploratory analysis	

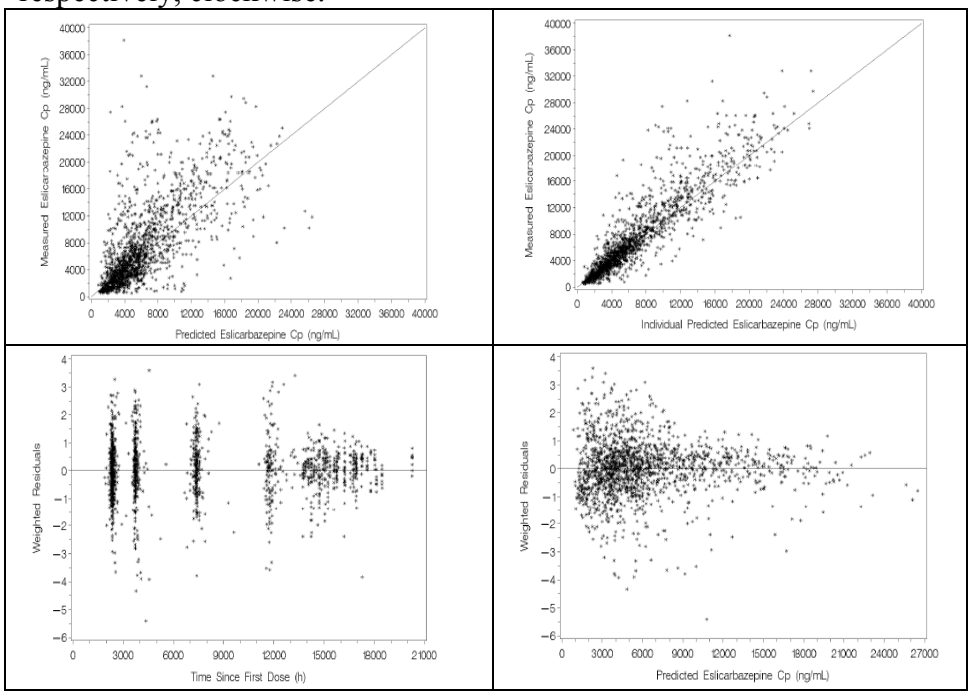
APPENDIX

1. The parameter estimates from the sponsor's final Population PK model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	3.88	4.4	43.13	22.7
V/F (L)	89.3	9.2	55.05	41.9
ka (h^{-1})	1.04	12.2	NE	NA
Effect of carbamazepine dose on CL/F (L/h)[a]	0.818	13.1	NA	NA
Effect of valproate concentration on CL/F (L/h)[a]	-0.312	33.7	NA	NA
Effect of phenobarbital-like metabolic inducers on CL/F (L/h)[a]	1.01	17.7	NA	NA
Covariance term (IIV CL/F and IIV V/F)	0.201	35.1	NA	NA
RV (SD in log concentration units)	0.41	8.6	NA	NA
Minimum value of the objective function = -442.562				

Abbreviations: AED, antiepileptic drug; CL/F, apparent oral clearance; %CV, percent coefficient of variation; ka, first-order absorption rate constant; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean; V/F, apparent volume of distribution

2. Goodness-fit plot for the sponsor's final population PK model : observed concentration .vs. predicted concentration, observed concentration .vs. individual predicted concentration, weighted residual .vs. time, weighted residual .vs. predicted concentration, respectively, clockwise.



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3. The parameter estimates from population PK analysis for drug-drug interaction study.
- Carbamazepine

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Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	1.92	12.7	21.98	11.1
Change in CL/F (L/h) per unit of daily carbamazepine dose (mg)[b]	0.00328	7.6	NE	NA
Change in CL/F (L/h) per unit of daily phenobarbital dose (mg)[b]	0.00867	15.0	NE	NA
Change in CL/F (L/h) per unit of daily eslicarbazepine acetate dose (mg)[b]	0.00051	11.0	NE	NA
Power on ALT ratio	0.0568	5.2	NE	NA
Power on ALP ratio	-0.102	13.5	NE	NA
Additive RV (SD in µg/mL)	1.13	7.0	NA	NA
Minimum value of the objective function = 2597.689				

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CL/F, apparent oral clearance; %CV, percent coefficient of variation; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean.

[a] The equation to predict the typical carbamazepine CL/F in the *j*th patient is below:

$$CL/F_j = \left(1.92 + 0.00328 \times dose_{carbamazepine_j} + 0.00867 \times dose_{phenobarbital_j} + 0.00051 \times dose_{eslicarbazepine_j}\right) \times \left(\frac{ALT_j}{17}\right)^{0.0568} \times \left(\frac{ALP_j}{81}\right)^{-0.102}$$

Where:

$dose_{carbamazepine_j}$ = the daily dose of carbamazepine in the *j*th patient

$dose_{phenobarbital_j}$ = the daily dose of phenobarbital in the *j*th patient

$dose_{eslicarbazepine_j}$ = the daily dose of eslicarbazepine acetate in the *j*th patient

ALT_j = alanine aminotransferase in the *j*th patient where the median alanine aminotransferase is 17 U/L

ALP_j = alkaline phosphatase in the *j*th patient where the median alkaline phosphatase is 81 U/L

- Gabapentine

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	27.2	11.6	50.60	18.0
Ratio of $\sigma_{additive}$: $\sigma_{proportional}$	2.44	16.8	NA	NA
RV[b]	0.116	14.9	NA	NA
Minimum value of the objective function = 199.960				

Abbreviations: CL/F, apparent oral clearance; %CV, percent coefficient of variation; NA, not applicable; RV, residual variability; %SEM, percent standard error of the mean.

[a] The equation to predict the typical gabapentin CL/F in the *j*th patient is below:

$$CL/F_j = 27.2 \times \left(\frac{CrCL_j}{114.5}\right)$$

- Levetiracetam

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	6.55	5.6	49.8	19.4
Change in CL/F (L/h) due to eslicarbazepine co-administration	1.10	44.4	NE	NA
Power on CrCL ratio	0.806	27.0	NE	NA
Additive RV (SD in log concentration units)	0.40	16.0	NA	NA
Minimum value of the objective function = -67.829				

Abbreviations: CL/F, apparent oral clearance; CrCL, creatinine clearance; %CV, percent coefficient of variation; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean.

[a] The equation to predict the typical levetiracetam CL/F in the *j*th patient is below:

$$CL/F_j = \left(6.55 + 1.10 \times dose_{eslicarbazepine_j}\right) \times \left(\frac{CrCL_j}{109.2}\right)^{0.806}$$

- Phenobarbital

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	0.151	12.6	40.87	20.3
Change in CL/F (L/h) per unit of daily phenobarbital dose (mg)[b]	0.000869	13.6	NE	NA
Additive RV (SD in µg/mL)	4.21	21.9	NA	NA
Minimum value of the objective function = 1163.169				

Abbreviations: CL/F, apparent oral clearance; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean.

[a] The equation to predict the typical phenobarbital CL/F in the *j*th patient is below:

$$CL/F_j = 0.151 + 0.000869 \times dose_{phenobarbital_j}$$

- Phenytoin

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	1.19	7.7	65.8	10.2
Change in CL/F (L/h) per units of daily eslicarbazepine acetate dose (mg)[b]	-0.000106	14.0	NE	NA
Ratio of $\sigma_{additive}$: $\sigma_{proportional}$	8.00	20.9	NA	NA
RV[c]	0.0490	9.9	NA	NA
Minimum value of the objective function = 664.850				

Abbreviations: CL/F, apparent oral clearance; %CV, percent coefficient of variation; NA, not applicable; NE, not estimated; RV, residual variability; %SEM, percent standard error of the mean.

[a] The equation to predict the typical phenytoin CL/F in the *j*th patient is below:

$$CL/F_j = 1.19 - 0.000106 \times dose_{eslicarbazepine_j}$$

- Valproate

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)[a]	0.265	25.5	39.75	21.0
Change in CL/F (L/h) per unit of daily valproate dose (mg)[b]	0.000487	10.9	NE	NA
Change in CL/F (L/h) per unit of daily carbamazepine dose (mg)[b]	0.00027	28.1	NE	NA
Additive RV (SD in µg/mL)	12.85	15.0	NA	NA
Minimum value of the objective function = 4191.336				

Abbreviations: CL/F, apparent oral clearance; %CV, percent coefficient of variation; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean.

[a] The equation to predict the typical valproate CL/F in the jth patient is below:

$$CL/F_j = 0.265 + 0.000487 \times dose_{valproate_j} + 0.00027 \times dose_{carbamazepine_j}$$

Where:

$dose_{valproate_j}$ = the daily dose of valproate in the jth patient

$dose_{carbamazepine_j}$ = the daily dose of carbamazepine in the jth patient

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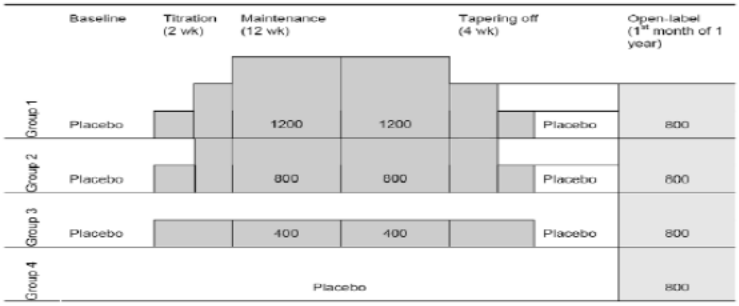
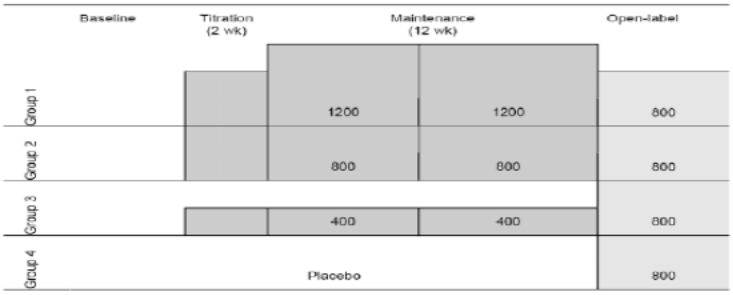
4. Study design :

BIA-2093-301



BIA-2093-302



BIA-2093-303

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APPENDIX II

OCPB FILING REVIEW

6 pages of Appendix II have been Withheld in Full immediately following this page as duplicate copy of the “Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA/BLA or Supplement” dated 07/16/2009 which can be found in the Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VENEETA TANDON
03/08/2010

KOFI A KUMI
03/08/2010

JOO YEON LEE
03/08/2010

YANING WANG
03/08/2010

YUXIN MEN
03/08/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		**Information**
NDA/BLA Number	22-416	Brand Name	
OCP Division (I, II, III, IV, V)	I	Generic Name	Eslicarbazepine Acetate or SEP-0002093 or BIA 2-093
Medical Division	120	Drug Class	• first-line dibenz[b,f]azepine antiepileptic • voltage-gated sodium channel (VGSC) blocker
OCP Reviewer	Veneeta Tandon (CP) Li Zhang (PG) Hao Zhu	Indication(s)	adjunctive therapy in the treatment of partial-onset seizures in adults
OCP Team Leader	Veneeta Tandon (Acting)	Dosage Form	Tablets, 400, 600 and 800 mg
Pharmacometrics Reviewer	Hao Zhu	Dosing Regimen	Initial: 400 mg QD for 1 week Maintenance: 800 MG QD Maximum: 1200 mg QD Titration: Increments of 400 mg at weekly internals
Date of Submission	3/29/09	Route of Administration	Oral
Estimated Due Date of OCP Review	11/1/09	Sponsor	Sepracor
Medical Division Due Date	11/29/09	Priority Classification	Standard
PDUFA Due Date	1/29/09		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clin. Pharm. and Biopharm. Information

SEP-0002093 (eslicarbazepine acetate, BIA 2-093), a novel voltage-gated sodium channel blocker is a third-generation, single-enantiomer member of the long-established family of first-line dibenz[b,f]azepine antiepileptic drugs (AEDs) represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). SEP-0002093 shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute but is structurally different at the 10,11-position. SEP-0002093 is prodrug that is rapidly and extensively metabolized (via hydrolases) to eslicarbazepine, the pharmacologically active moiety, and (R)-licarbazepine and oxcarbazepine in a (b) (4) which are also active; systemic exposure to the parent drug is negligible in humans. Eslicarbazepine is eliminated from the systemic circulation primarily by renal excretion: two thirds (67%) in the unchanged form and one third (33%) after conjugation with glucuronic acid. In total, eslicarbazepine unchanged and its glucuronide form corresponds to 92% of total drug material excreted in urine. Minor metabolites in urine were (R)-licarbazepine, oxcarbazepine and the glucuronide forms of SEP-0002093, eslicarbazepine, (R)-licarbazepine and oxcarbazepine.

There are 22 Phase I studies in healthy subjects or special populations, two Phase II studies (Study 201 and 202) and three Phase III studies (Study 301, 302 and 303). In addition, three Phase II studies were performed in adults with bipolar disorder.

The Clinical Pharmacology program consists of the following studies:

PK in healthy subjects:

1. SD Ascending Doses 200-1200 mg (Study 01)
2. MD Ascending Doses, 200-1200 QD for 8 Days (Study 02)
3. SD and MD Study: 1800 and 2400 mg SD, 1800 and 2400 mg QD for 7 days (Study 113)
4. MTD Study: 3000 mg and 3600 mg QD for 2 days (Study 118)
5. MD Study: ESL and metabolites PK, 900 and 450 mg (Study 115)

Relative BE studies:

1. BE of Tablets/Suspension, 800 mg, 4x200 mg (Study 109)
2. SD Study: ESL and OXC PK, 900 mg (Study 104)
3. MD Study: ESL and OXC PK with 8 days dosing, 900 mg QD, 450 mg BID (Study 110)

Bioequivalence Studies:

1. Clinical trial formulation vs TBM formulation, Test: 400 mg 600 and 800 mg(Study 122)
   Reference: 400mg, 600 mg and 800mg***

***the TBM formulation FP is not used in the phase 3 studies. A BE study is conducted between FP and FN, FK, FC formulations

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Food Effect Studies:

1. Food effect: 800 mg (Study 103)
2. Food effect and Dosage Strength Proportionality: 800 mg, 2x400 mg (Study 117)

PK in Patients:

Patient PK is assessed in Phase 2 (Studies 201 and 202) and Phase 3 (Studies 301, 302, 303). The Phase 3 studies also look at dose proportionality,

Intrinsic factors:

1. Effect of age and sex (Study 105)
2. Hepatic Impairment (Study 111)*** No dose adjustment in mild/mod, not studied in severe
3. Renal Impairment (Study 112): Dose adjustment recommended in moderate and severe

*** No mass balance study, but using AUC0-24, determined that 91% of all circulating entities is eslicarbalzepine and have urinary levels of all species is measured in this study.

Extrinsic Factors (Drug Interactions)

1. Digoxin (Study 107)
2. Warfarin (Study 108)
3. Oral Contraceptive (Study 114)
4. Lamotrigine (Study 119)
5. Topiramate (Study 120)
6. Phenytoin (Study 121 and 106)

Pop PK evaluated: carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, topiramate, and valproate

In Vitro:

1. Protein Binding (N=3)
2. Inhibition Potential (N=1) CYP 2C8 not evaluated
3. Induction Potential (N=4)
4. DDI (effect of inhibitory effect of other antiepilpetics on Parent metabolism) (N=1)

Other:

1. Population PK (2 reports)
2. PK-PD (Phase 3 studies: 1 report)
3. Thorough QTc Study (Study 116)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**x**	**3**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**2**		
multiple dose:	**x**	**5**		
Patients-				
single dose:				
multiple dose:	**x**			**Phase 2 and 3 studies**
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**		
fasting / non-fasting multiple dose:	**x**			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**6**		
In-vivo effects of primary drug:	**x**			
In-vitro:	**x**			
Subpopulation studies -				
ethnicity:	**x**			
gender:	**x**	**1**		
pediatrics:				
geriatrics:	**x**			
renal impairment:	**x**	**1**		
hepatic impairment:	**x**	**1**		
PD -				
Phase 2:	**x**			
Phase 3:	**x**			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**x**	**1**		
Population Analyses -				
Data rich:				
Data sparse:	**x**	**2**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			
Literature References	**x**			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Total Number of Studies	**22 PK 4 IN VITRO 4 ASSAY 2 POP PK 1 PK-PD**			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	x			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Request to the sponsor:

1. Assay validation report for lamotrigine (Study 119) and topiramate (Study 120) could not be located. Please provide location in the EDR. Please submit if not provided in the original submission.
2. Assay validation for other AEDs evaluated in the population analysis should also be submitted.

DSI Inspection Requested:

DSI Inspection of the pivotal BE study is requested as the TBM formulation is not used in any Pivotal Clinical Studies. The bioequivalence was assessed in Study 122.

The Clinical and Analytical Sites for Inspection are attached in the following Page.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

For BE Study 122:

CLINICAL FACILITIES: Algorithme Pharma Inc.
1575 Henri-Bourassa Blvd. W., 6th floor
Montreal, Quebec, Canada
H3M 3A9
and
Algorithme Pharma Inc.
1200 Beaumont Ave.
Mount-Royal, Quebec, Canada
H3P 3P1

Clinical Director:
Study Manager: (b) (4)

QUALIFIED INVESTIGATOR: Eric Sicard, M.D., Clinical Investigator
Algorithme Pharma Inc.
Telephone: (514) 858-6077
Fax: (514) 380-5261

MEDICAL LABORATORY: (b) (4)

ANALYTICAL LABORATORY: (b) (4)

Vice-President, (b) (4) (b) (4)

STATISTICAL/PK FACILITY: (b) (4)

Senior Clinical Research Scientist:
Director, Biometrics and Statistics:
Vice-President of Scientific and Regulatory Affairs: (b) (4)

Table 4: Composition of Clinical Trial Formulations FN and FK

Starting material	Quantity (mg/ tablet)		Function	Standard Reference
	FN	FK		
Eslicarbazepine acetate	400.0	600.0	Active substance	In-house monograph
(b) (4)			(b) (4)	Ph. Eur.
Povidone				Ph. Eur.
Croscarmellose sodium				Ph. Eur.
(b) (4				Ph. Eur.
Magnesium stearate				Ph. Eur.

* does not appear in the finished product

To-Be Marketed Formulation:

Table 1: Compositions of Eslicarbazepine Acetate 400, 600 and 800 mg Tablets

Strength	**400 mg**	**600 mg**	**800 mg**		
Component	**Quantity (mg/ tablet)**			**Function**	**Reference**
Eslicarbazepine acetate	400.0	600.0	800.0	Active substance	PT-QCMN1
Povidone (b) (4)				(b) (4)	USP
Croscarmellose sodium					NF
(b) (4)					USP
Magnesium stearate					NF
Tablet weight (target in mg)	467	700	933		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Veneeta Tandon
7/16/2009 08:30:54 AM
BIOPHARMACEUTICS