Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Lamotrigine
PRODUCT (Brand Name):	LAMICTAL XR
NDA:	22-115
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	25, 50, 100 or 200 mg
INDICATION:	Adjunctive therapy for partial onset seizures With or without generalization in patients ≥ 13 years
NDA TYPE:	1S
SUBMISSION DATES:	11/22/06, 3/22/07, 6/20/07, 8/1/07
SPONSOR:	GSK
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
PHARMACOMETRICS REVIEWER	Joga Gobburu, Ph.D.
PHARMACOMETRICS TEAM LEADER	Yaning Wang, Ph.D
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

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1.0 EXECUTIVE SUMMARY

Lamotrigine (LAMICTAL®, 3, 5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine anticonvulsant.

This application N22-115 is for a new dosage form as an extended release formulation of lamotrigine (LAMICTAL XR) for adjunctive treatment of partial seizures with or without secondary generalization in patients 13 years of age or older for once daily dosing.

LAMICTAL® was first approved in the US in December 1994 (NDA 20-241) for adjunctive treatment of partial seizures in adults. Two immediate-release formulations (LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets) are FDA-approved for these indications as twice daily administrations.

Following is the chronological order for all approvals for LAMICTAL®:

December 1994: Original NDA for adjunctive treatment of partial seizures in adults
August 1998: Adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in pediatric (2-16 years of age) and adult

	subjects (along with a chewable dispersible tablet formulation; NDA 20-764)
December 1998:	conversion to monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug (EIAED)
January 2003:	As adjunctive treatment for partial seizures in pediatric subjects (2-16 years of age)
June 2003:	long-term management of mood episodes in subjects with Bipolar I disorder
January 2004:	conversion to monotherapy from valproate (VPA) in adult subjects with partial seizures
September 2006:	primary generalized tonic-clonic (PGTC) seizures in adults and pediatric subjects (2-16 years of age)

Lamotrigine extended-release (lamotrigine XR) is a new, enteric coated, formulation for a once daily dosing regimen.

The clinical development program for lamotrigine XR consists of seven Phase I Clinical Pharmacology studies conducted in healthy volunteers (LAM10007, LAM10004, LAM10005, LAM100014, LAM100017, LAM105537 and LAM102611), and one Phase I Study conducted in patients with epilepsy (LEP103944). The main clinical pharmacology studies mainly evaluated the single and multiple dose pharmacokinetics, dose proportionality, dosage strength equivalency, food effect and the conversion from the immediate release dosage form to the proposed extended release dosage form and a drug interaction study with esomeprazole. The other studies were exploratory and formulation development in nature. In addition to these studies, blood samples for population pharmacokinetic analysis were collected in one Phase III Clinical Study evaluating lamotrigine XR as adjunctive treatment for partial seizures in patients 13 years of age and older (LAM100034). A thorough QTc study was also conducted using the immediate release dosage from.

The main issues identified during the review process were (i) potential lower lamotrigine's effect in US versus non-US patients; (ii) Limited number of pediatric patients between 13-17 yrs (N=7 on lamotrigine in study LAM100034); (iii) change of dissolution specifications.

These issues have been discussed from the Clinical Pharmacology and Biopharmaceutics perspective in the ‘Overall Summary of Findings’ and the ‘Question Based Review’ sections on the Review.

1.1 RECOMMENDATION

This NDA 22-115 is acceptable from a clinical pharmacology standpoint provided the Labeling changes and the Dissolution Specifications as proposed by the Agency are accepted by the sponsor.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

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

Exposure-Response for Effectiveness:
Exposure-response analysis of the pivotal clinical efficacy study LAM100034 (with sparse samples) and the supportive conversion (IR to XR) study LEP104944 (with intense sampling) using non-linear mixed effects modeling, showed that at the end of the treatment period there was a decrease in seizure frequency with increasing lamotrigine concentration.
The concentration effect relationship was not affected by the age, race or sex of the patient, nor was it affected by the concomitant AED therapy. However, a country effect (US vs Non US) was identified in the statistical analysis. On evaluation of the plasma concentration data, it was observed that:

(i) The lamotrigine concentrations in the US and non-US patients were overlapping,
(ii) A clear exposure-response for both US (N=65) and all (both US and Non US) (N=192) patients was also observed. The slope of the concentration-response rate curve is significant for both populations (US=0.0493; all=0.029);
(iii) The US sites have a slightly higher placebo response than non-US (33% in US and 23% in Non US for % reduction from baseline seizure frequency). This might have contributed to the lack of significant drug effect (primary endpoint) in the US patients.
(iv) Since lamictal IR is approved based on US trials and the relative bioavailability of the XR formulation compared to the IR formulation is 90%; the IR and XR will produce similar effects at comparable concentrations.

Although an age effect was not identified in the exposure-repsonse analysis, it should be noted that there were a total of 16 children between the ages 13-18 years (7 on lamotrigine and 9 on placebo) in the pivotal clinical trial that had sparse PK samples (4-6/subject). Lamotrigine concentrations in these subjects were not different from the adults. Although there are few subjects between the age range of 13-18 years, additional PK study is not necessary in this age group because:

(i) concentrations (and dosing) were similar to the adults and there were at least 4-6 samples per subject;
(ii) effectiveness of lamotrigine IR in the age range 12-18 years has been established and dosing in partial seizures for the IR formulation is same for ages 12 and older;
(iii) relative bioavailability to the IR formulation in patients is known (overall 90% relative BA), hence overall the exposures are not expected to be very different.

Exposure-Response for Safety:
Due to the low frequency of adverse events in the pivotal study LAM100034 it was not possible to establish any relationship between lamotrigine exposure and adverse events such as dizziness, ataxia, diplopia and nausea.

Effect on QTc prolongation:
Please refer to the review by the IRT for QTc analyses.

General Pharmacokinetics (ADME characteristics) of LAMICTAL XR:

Absorption from the ER dosage form is slower as compared to the IR dosage form. Median peak concentrations (T_{max}) are reached at 10-14 hours post dose from the ER dosage form compared to about 1-5 hours from the IR dosage form in healthy volunteers. In epilepsy patients, the median time to peak concentration (T_{max}) following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone, 9 to 11 hours in patients taking VPA, and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA.
The distribution, metabolism and elimination characteristics are the same as that of the

IR dosage form, with the half-life also being similar with the two dosage forms (about 30 hours in healthy subjects and depends on the concomitant AED in patients).

Single dose and multiple dose pharmacokinetics:
Following repeat dose administration of the 25 mg XR tablet in comparison to single dose of 25 mg XR tablet of lamotrigine in healthy volunteers, there was an approximate 3-fold increase in Cmax and AUC(0-24). There was evidence of auto-induction as mean terminal phase half-life decreased from 44 h for a single dose to 39.4 h following repeat dosing. This finding is consistent with that observed with lamotrigine IR. The median time to Cmax (tmax) following repeat dosing of lamotrigine XR was 10 h compared to a median tmax of 20 h for a single dose.

PK Comparisons and Conversion from IR to XR lamotrigine:

The PK comparisons on switching from the lamotrigine IR to the XR dosage form in patients was done in the presence of 3 AED groups (inducers, inhibitors and neutrals) in a study with about 12 subjects in each group. These comparisons showed that:

- The steady-state trough concentrations for Lamotrigine XR were either equivalent to or higher than those of lamotrigine IR depending on concomitant AED.
- A mean reduction in the lamotrigine Cmax by 11-29% was observed for lamotrigine XR compared to lamotrigine IR depending on concomitant AED, however some subjects on enzyme inducing AED had reduction in Cmax of 45-77% (N=3) as well. In general the lower Cmax with extended release formulation resulted in a decrease of peak to trough fluctuation in serum lamotrigine concentrations.
- The mean fluctuation index was reduced by 17% in patients taking enzyme-inducing AED, 34% in patients taking VPA and 37% in patients taking neutral AEDs.
- Lamotrigine XR and lamotrigine IR regimens were approximately similar (6% decrease) with respect to AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR based on means. However some subjects (N=2) on EIAEDS had a 57-70% reduction in AUC(0-24ss). Therefore, these subjects may not have the same therapeutic response on conversion to the XR formulation, dose may need to be titrated to therapeutic response.

These comparisons are shown in the following Table:

Table Adjusted Steady-State Geometric LS Mean Ratio and 90% CI of Dose Normalized Lamotrigine Steady-State PK Parameters XR vs. IR

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
Cτ/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

The PK comparisons in healthy volunteers showed that:

- In terms of dose-normalized AUC(0-τ), the 50 mg, 100 mg and 200 mg EC-MR formulations had a mean relative bioavailability of 81 %, 97% and 91%, respectively, compared to the IR formulations at the same daily dose.
- Steady-state trough concentrations for all three doses were close to 100 % in comparison to the IR formulation.
- In terms of Cmax, the maximum concentration of the EC-MR formulation was lower than the IR by approximately 10-30 % across the dose range.

These results are consistent with that seen in patients.
Based on these observations, patients may be converted directly from immediate-release lamotrigine to LAMICTAL XR Tablets. The initial dose of LAMICTAL XR should match the total daily dose of immediate-release lamotrigine on the previous day. However, patients on concomitant enzyme inducing agents may need to be monitored and dose titrated according to therapeutic response.

Dose proportionality: Dose proportionality of lamotrigine was observed following repeat oral administration over the dose range of 50-200 mg QD dosing of the EC-MR formulation, however a slightly less than proportional increase with increasing dose was observed over the dose range of 25-200 mg dose range of the EC-MR formulation. Dose proportionality has not been studied throughout the labeled dose range of extended release formulation (although sparse sampling data are available).

Pharmacokinetics in patients: The steady-state pharmacokinetics of lamotrigine in patients with epilepsy in the "neutral group" (i.e. in subjects not on inducers or inhibitors) were similar to those observed in healthy volunteers.

Special Populations: No new studies in special populations have been conducted with the extended release form. In the population analysis with the XR formulation age was not a significant covariate. However, there were only 7 subjects between the ages 13-18 that were on active treatment and 9 on placebo in the pivotal clinical trial LAM10034. The lamotrigine concentrations in these 7 subjects (ages 13-18) were similar to that of the adults based on 4-6 samples per subject. The dosing recommendations and or adjustments remain the same as that evaluated for the IR dosage form.

Drug-drug Interactions: No new drug interaction studies have been conducted with LAMICTAL XR.

Biopharmaceutics: The following are the Biopharmaceutics aspect of the application:
Bioequivalence: A bioequivalence study was not necessary as the commercial formulation was used in the pivotal efficacy study as well as the pivotal clinical pharmacology studies (dose proportionality and food effect)
Dosage strength Equivalency: The following dosage strengths of the ER tablets are pharmacokinetically equivalent:

- 2x25mg EC-MR tablet vs. 1x50mg EC-MR tablet
- 2x50mg EC-MR tablet vs. 1x100 mg EC-MR tablet
- 2x100mg EC-MR tablet vs. 1x200mg EC-MR tablet

Food Effect: Food effect study on the 200 mg strength showed that the AUC and Cmax were similar under fed and fasted conditions. In the clinical trials, lamotrigine XR was dosed without regards to food and this is the proposed dosing recommendation.
IVIVC: The IVIVC is not validated and cannot be used at this time, until further data are submitted.

(b) (4)

(b) (4)

Effect of ethanol on dissolution: Ethanol did not have a significant impact on the release rate of Lamotrigine Extended Release Tablets and there was no evidence of 'dose dumping'.

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

Joga Gobburu, Ph.D
Pharmacometrics

Team Leader: Ramana Uppoor, Ph.D._____

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

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Lamotrigine extended release tablets are round biconvex film coated tablets, printed on one face in (b) (4) ink with "LAMICTAL" (b) (4) and "XR 25", "XR 50", "XR 100" or "XR 200" (b) (4). Tablets will also be distinguished by color; yellow for 25mg, green for 50 mg, orange for 100 mg and blue for 200 mg tablets.

Dosage Form/Strengths: Lamotrigine XR is an extended release tablet to be marketed as 25, 50, 100 and 200 mg tablets

Indication: Adjunctive therapy for partial onset seizures with or without secondary generalization in patients ≥ 13 years of age.

Dosage and administration (Sponsor's Proposed):

Once a day (b) (4), using the same dosing recommendations (total daily dose) as currently approved for lamotrigine IR (Table). (b) (4)

Table: Proposed Dosing Recommendations for Lamotrigine XR

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone and Not Taking Valproate
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance Range (Week 8 and onward)	150-250 mg every day	200-400 mg every day	400-600 mg every day

Pharmacologic Class: Phenyltriazine anticonvulsant

Chemical Name: 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

Physical Characteristics: (b) (4)

Mechanism of action: The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. It is thought to have an effect on the sodium channels.

Formulation:

A few clinical pharmacology studies were conducted using prototype formulations to select the appropriate formulation of the Lamotrigine extended release tablets:
A brief overview of the formulation development is given below:

- LAM10007 investigated the regional gastrointestinal absorption of lamotrigine to evaluate the feasibility of developing a controlled release formulation. Results from this study indicated that a controlled release product for lamotrigine was feasible due to the maintained absorption throughout the length of the gastrointestinal tract.

(b) (4)

(b) (4)

(

Formulation development work was also performed to produce a 100 mg tablet by a (b) (4) to deliver the drug at a similar rate as the 200 mg tablet. To achieve this, the same matrix core as the 200 mg tablet was used, (b) (4)

.

(b) (4)

Table: Summary Table of Quantitative Formula for the lamotrigine XR tablet: 25, 50, 100 and 200 mg

Component	Quantity (mg per tablet)				Function
(b) (4)	25 mg	50 mg	100 mg	200 mg	
Lamotrigine	25.0	50.0	100.0	200.0	Active
Lactose Monohydrate Hypromellose (b) (4) 4000 m Pas Hypromellose (b) (4) 100 m Pas Silicon Dioxide Magnesium Stearate Purified Water	(b) (4)				(b) (4)
(b) (4)					
Opadry Yellow (b) (4)	(b)	-	-	-	(b) (4)
Opadry Green (b) (4)	-	(b)	-	-	
Opadry Orange (b) (4)	-	-	(b) (4)	-	
Opadry Blue (b) (4)	-	-	-	(b) (4)	
Purified water	-	-	-	-	
(b) (4)					
Methacrylic Acid Copolymer Dispersion Type C Triethyl Citrate Glycerol Monostearate Polysorbate 80 Purified water	(b) (4)				(b) (4)
Printing ink					
Opacode (b) (4)	(b) (4)				(b) (4)
Total unit weight	324.9	324.9	430.7	430.7	-

The tablets have an aperture drilled through the coats on both faces of the tablet to enable a controlled release of drug in the acidic environment of the stomach. An illustration of the tablet design is presented in the following Figure:

Figure: Formulation Design Schematic of a Lamotrigine Extended Release Tablet

(b) (4)

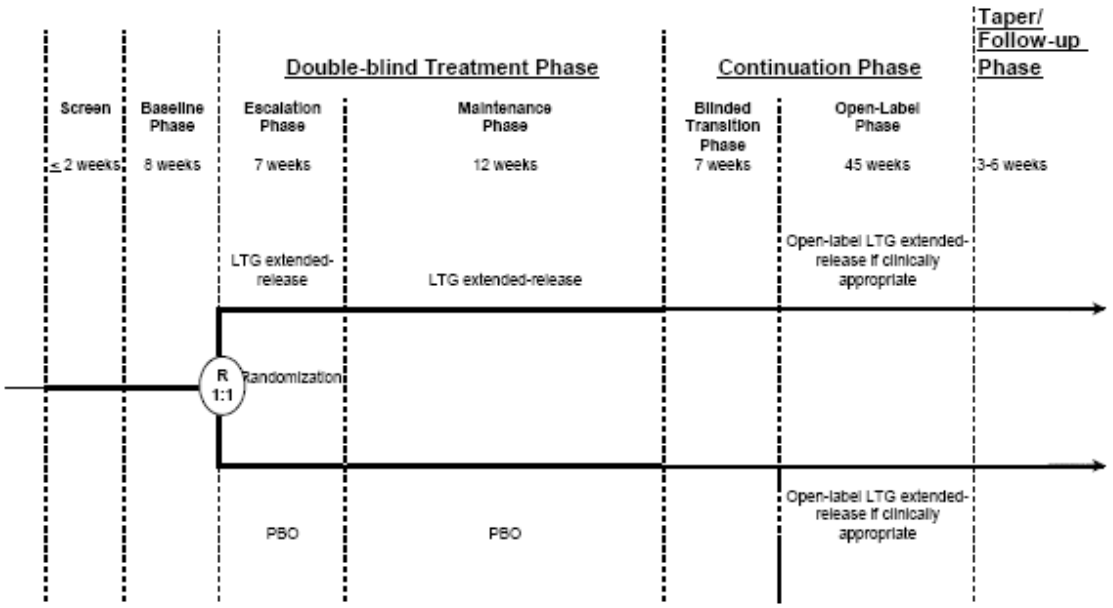
2.2 GENERAL CLINICAL PHARMACOLOGY

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

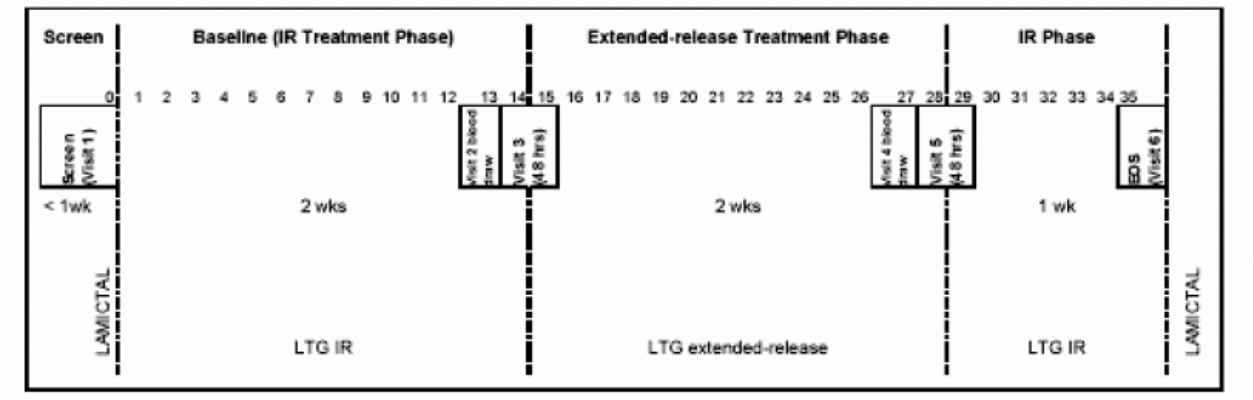
This application for lamotrigine XR tablets consists of two clinical studies in subjects with epilepsy: LAM100034 (adjunctive treatment of partial seizures in subjects ≥13 years of age), and LEP103944 (open-label study evaluating the conversion from immediate-release to extended-release lamotrigine). LAM100034 is the pivotal clinical effectiveness study supporting this application, while LEP103944 provides supporting information for conversion from immediate-release to extended-release lamotrigine.

LAM100034 was a double-blind, randomized, parallel-group study evaluating the efficacy, safety, pharmacokinetics and health outcomes of once daily lamotrigine XR, as adjunctive therapy, compared to placebo for the treatment of partial seizures.

The maximum duration of the study was approximately 87 weeks, divided as follows:



LEP103944 was an open-label study designed to characterize the pharmacokinetic (PK) profile of lamotrigine when administered as extended-release once daily compared to the current formulation (lamotrigine IR) administered twice daily. The double-conversion study had three phases after screening: a baseline with lamotrigine IR, a treatment phase with lamotrigine XR and a last phase with lamotrigine IR.



In addition to these, the clinical development program for lamotrigine XR consists of seven Phase I Clinical Pharmacology studies conducted in healthy volunteers (LAM10007, LAM10004, LAM10005, LAM100014, LAM100017, LAM105337 and LAM102611)

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

Primary Endpoint:

- Percentage change from Baseline in partial seizure frequency during the entire Double-Blind Treatment Phase.
  Average weekly seizure frequency, defined as the frequency of seizures divided by the number of study weeks in the Baseline or analyzed treatment time period contributing to the frequency counts, was computed for each subject in order to derive the percent change from Baseline in seizure frequency value.
  Percent change from baseline was computed as ((Baseline - Treatment)/Baseline)*100, where a positive value indicates a reduction from Baseline in seizure frequency.

Secondary Endpoints:

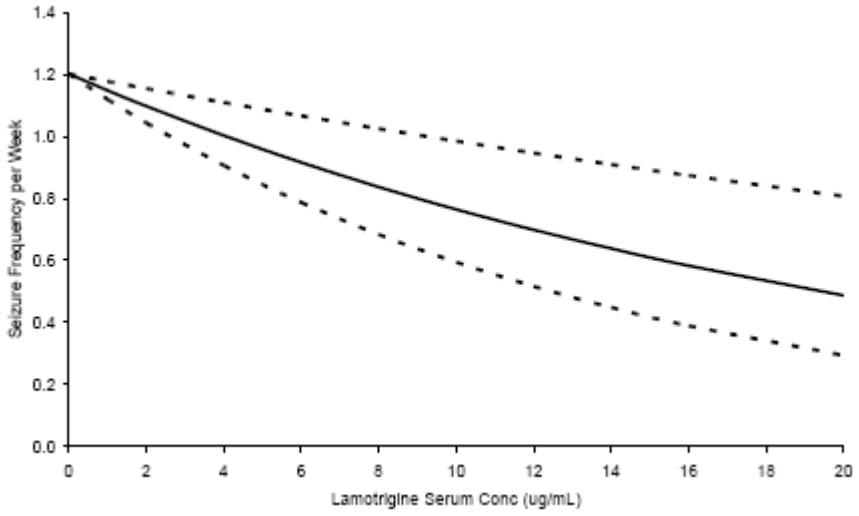
- Median percent change from Baseline in partial seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase
- Proportion of subjects with ≥25%, ≥50%, ≥75% or 100% reduction in partial seizure frequency during the entire Double-Blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase
- Time to ≥50% reduction in seizure frequency
  Time to ≥50% reduction in seizure frequency (in days) will be calculated from the first day of study medication to the day at which a ≥50% reduction from baseline in seizure frequency is observed. Only subjects who maintain the ≥50% reduction in seizure frequency for the remainder of the Treatment Phase will meet this endpoint.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

Exposure response analysis on the extended release formulation was conducted on the pivotal clinical efficacy study (LAM100034 (sparse samples) and the supportive conversion study LEP104944 (intense sampling), using non-linear mixed effects modeling and accounted for a placebo/time effect, baseline and study effects as well as the lamotrigine concentration. Due to the different study design of the two studies, the percentage change in seizure frequency was available only in study LAM100034, therefore the primary analysis used the seizure frequency rather than its change from baseline.

This analysis showed that at the end of the study there was a decrease in seizure frequency with increasing lamotrigine concentration (see Figure below)

Figure: Predicted Relationship between Seizure Frequency at the End of the Study versus Lamotrigine Serum Concentration (mean 90% CI).

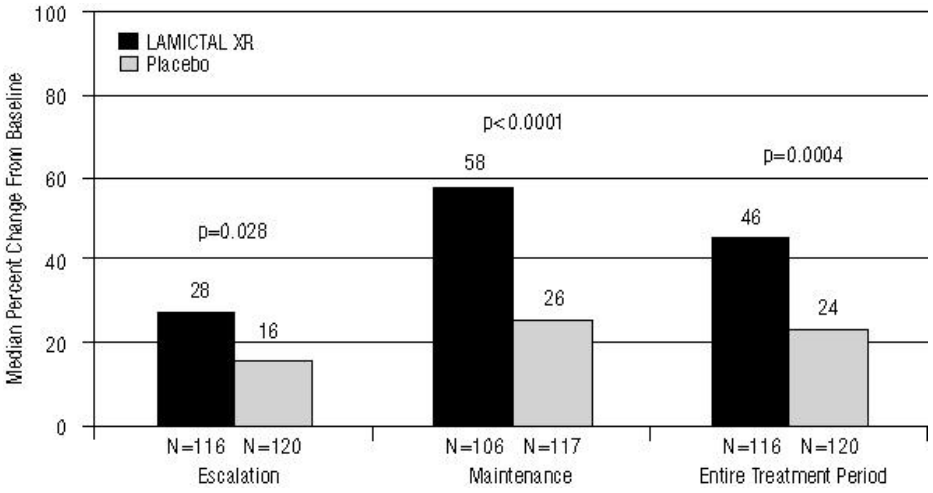


The concentration effect relationship was not affected by the age, race or sex of the patient, nor was it affected by the concomitant AED therapy.

It should be noted that the relationship between lamotrigine systemic exposure and seizure frequency has not yet been fully evaluated during the clinical development of the immediate release formulation of lamotrigine.

According to the sponsor the median seizure frequency is shown in the following Figure:

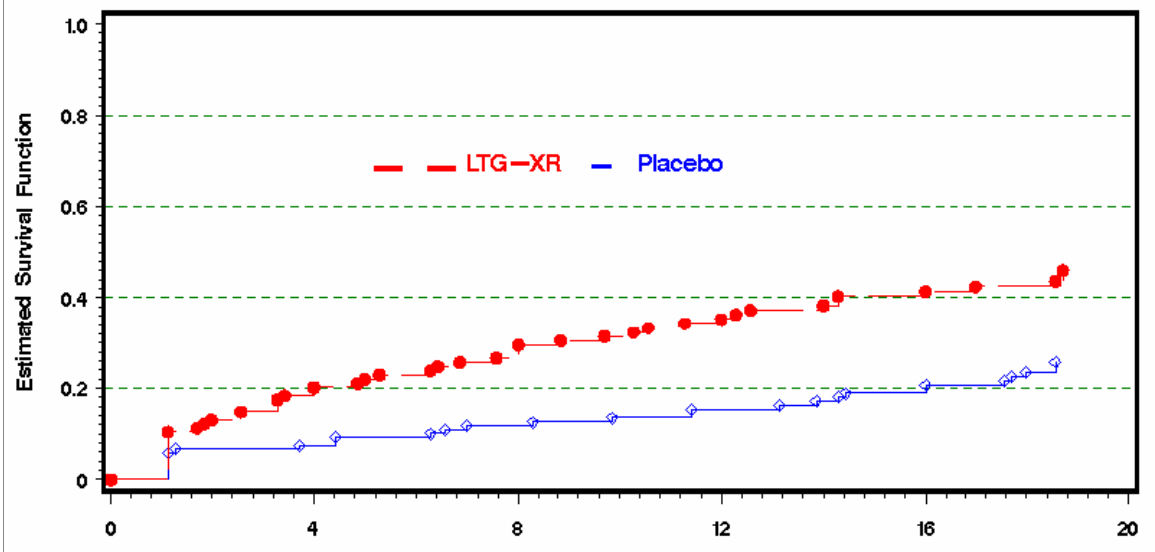
Figure: Median Reduction in Weekly Partial Onset Seizures



The percentage of subjects who showed a ≥50% reduction in partial onset seizure frequency over the entire double-blind treatment phase was significantly greater in the

group treated with LAMICTAL XR compared with placebo (42% vs 24% respectively, p = 0.0037). The time to achieve and maintain a ≥50% reduction in partial onset seizure frequency was significantly shorter for the group treated with LAMICTAL XR compared with placebo (p = 0.0007). Statistical significance was evident at Day 18 (p = 0.04).

Figure: Time to 50% Reduction in Seizure Frequency (ITT Population: Study LAM100034)



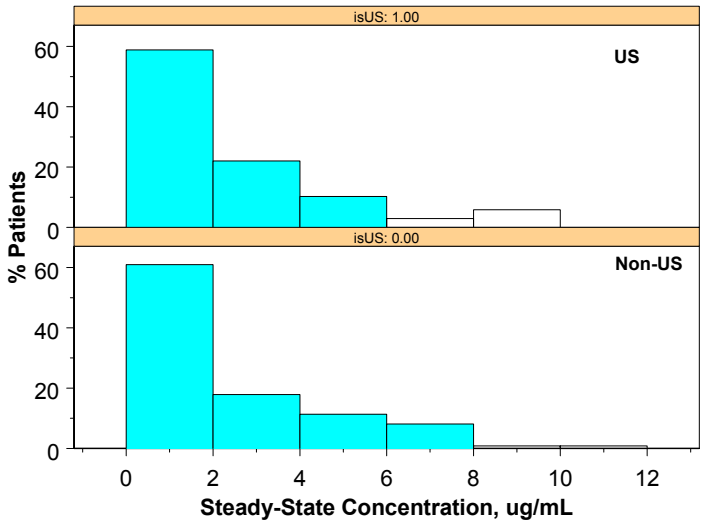
Subjects At Risk					
LTG-XR 116	91	77	67	56	0
Placebo 120	110	101	94	89	0

Note: Statistical Significance was seen as early as Day 18 (p=0.0448).

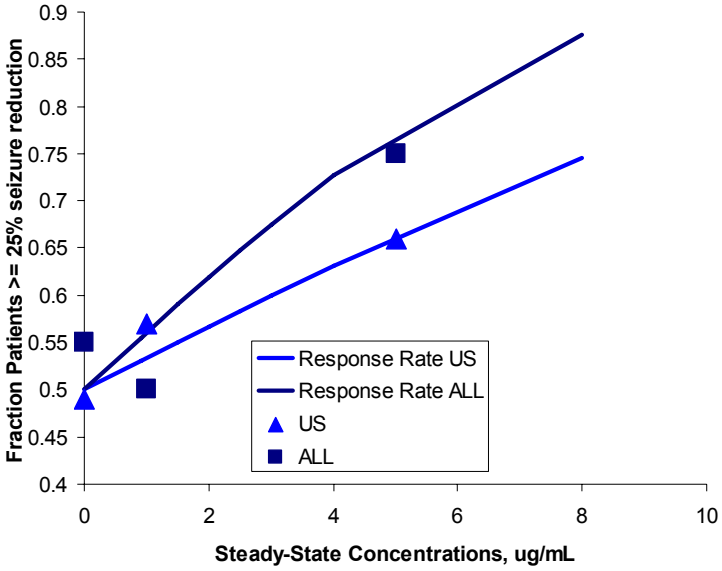
US versus Non-US

The pivotal trial LAM100034 was conducted at multiple sites across the world. The statistical analyses indicates that the drug effect (baseline, placebo corrected) is diminished in the US patients compared to non-US. Within the non-US trials there is a large variability in the mean drug effects. Another difference between the sites is the placebo response; US sites have a slightly higher placebo response than non-US. This might have contributed to the lack of significant drug effect (primary endpoint) in the US patients. We reviewed the lamictal steady-state average concentration – response rate (>=25% reduction in seizures from baseline; a pre-specified secondary endpoint) by region for the entire treatment duration (double-blind phase).

a. The graph below shows the distribution of the average steady-state concentration between US (top panel) and Non-US (lower panel) sites. The concentrations in US and non-US patients are overlapping.



b. The graph below shows a clear exposure-response for both US (N=65) and all (both US and Non US) (N=192) patients. The slope of the concentration-response rate curve is significant for both populations (US=0.0493; all=0.029). We did not conduct analysis of non-US alone as non-US included geographically varied sites (Russian Federation, India, Korea). Further separation of non-US sites by region will not render interpretable results due to small sample sizes per site.



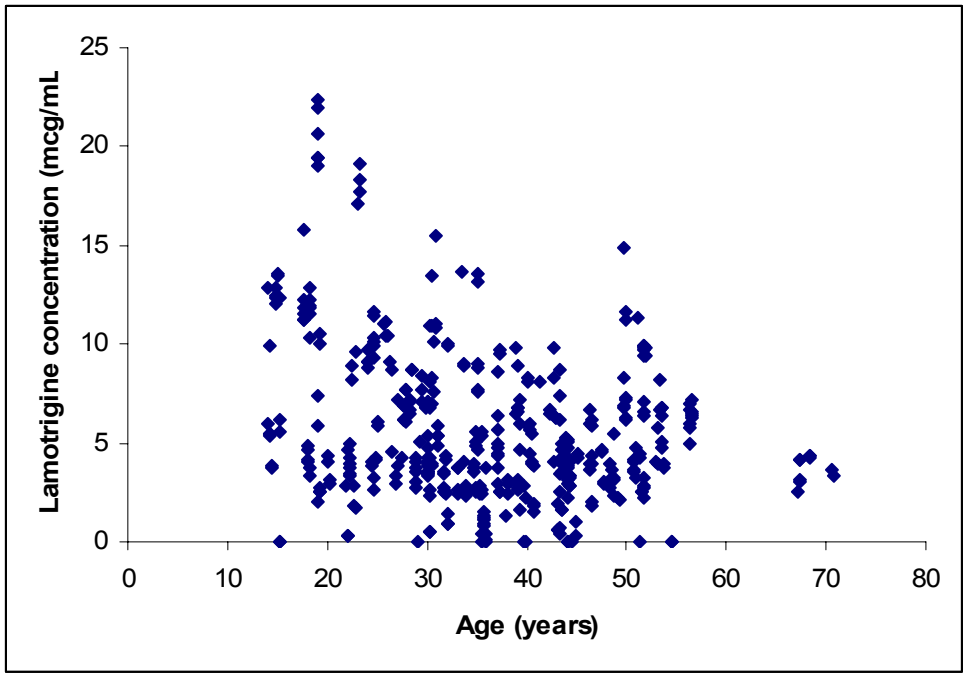
c. Lamictal IR and XR result in concentrations in the same range. Lamictal IR is approved based on US trials. Given the concentration-response relationship across multiple endpoints (continuous seizure reduction and response rate),

these two formulations of the same active moiety will produce similar effects at comparable concentrations.

2.2.4 Is there substantial evidence of effectiveness in children ages 13-18 years?

In the pivotal clinical study LAM10034, there were a total of 16 children between the ages 13-18 years (7 on lamotrigine and 9 on placebo). In these 7 children on treatment, lamotrigine concentrations based on sparse samples (4-6 samples per subject) were similar to that of the adults, as shown in the Figure below:

Figure: Effect of age on lamotrigine plasma concentrations



Although there are few subjects between the age range of 13-18 years, additional PK study is not necessary in this age group because (i) concentrations (and dosing regimen) were similar to the adults and there were at least 4-6 samples per subject; (ii) effectiveness of lamotrigine IR in the age range 12-18 years has been established and dosing in partial seizures for the IR formulation is same for ages 12 and older; (iii) relative bioavailability to the IR formulation in patients is known (overall 90% relative BA), hence overall the exposures are not expected to be very different.

2.2.5 What are the characteristics of exposure-safety relationships?

Due to the low frequency of adverse events in the pivotal study LAM100034 it was not possible to establish any relationship between lamotrigine exposure and adverse events

such as dizziness, ataxia, diplopia and nausea.

In study LAM10034 no incidence of serious rash was observed. The underlying relationship between systemic exposure to lamotrigine and adverse events, in particular rash, has not been established. However, the risk of non-serious rash appears to be increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded. It is believed that the risk of severe, potentially life-threatening, rash also may be increased by (1) co-administration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine (based on the approved IR labeling).

2.2.6 Are the proposed dosage regimens for partial seizures adequately supported by the clinical trial and consistent with the dose-response relationship?

The proposed dose escalation regimen for lamotrigine XR as adjunctive therapy for treatment of partial seizures with or without secondarily generalized seizures is based on the three dosing regimens used in the Study LAM100034. It is proposed that lamotrigine XR formulation will be orally administered, on a once daily basis, and titrated to efficacy, using the same starting dose and dose titration, and comparable maintenance doses as currently approved for lamotrigine IR.

These doses for the maintenance period seem to be a little higher than that approved for the IR regimen. (Please see Table below for differences)

Table: Doses for the maintenance period (in patients age 12 and over)

	For patients taking valproate	For patients taking neutral AEDs	For patient taking EIAEDs
LAMICTAL XR proposed	150-200 mg everyday	200-400 mg everyday	400-600 mg everyday
LAMICTAL (IR)	100-200 mg everyday	225-375 mg everyday	300-500 mg everyday

These differences will be evaluated by the reviewing Medical Officer to see if adequate number of patients in Study LAM100034 have received these higher doses and that these higher doses are equally safe compared to the approved doses for the immediate release, although Cmax's will be significantly lower for the XR formulations in patients on EIAEDs.

2.2.7 Is the proposed dose conversion from the lamotrigine IR to the LAMICTAL XR acceptable?

The sponsor recommends that patients may be converted directly from immediate-release lamotrigine to LAMICTAL XR Extended-Release Tablets. The initial dose of

LAMICTAL XR should match the total daily dose of immediate-release lamotrigine on the previous day.

The sponsor proposed recommendations for converting subjects from lamotrigine IR to lamotrigine XR is based on study LEP103944 which evaluated the within-subject conversion of lamotrigine IR to lamotrigine XR in adult subjects with epilepsy. The lamotrigine steady-state relative bioavailability was evaluated in 3 groups of patients receiving different concomitant AEDs (enzyme inducers, inhibitors and neutrals). The following was the duration of the IR and XR arms in this study:

Phase	Duration of Phase	Purpose
Screen	<1 week	Determine eligibility
Baseline (IR Treatment Phase)	2 weeks	Continue on twice daily LTG-IR
Extended-release Treatment Phase	2 weeks	Switch to once daily LTG extended-release
IR Phase	1 week	Switch back to twice daily LTG-IR
(At EOS visit)		Switch to commercially available LTG

The following Table shows the steady state comparisons of the IR and the XR treatment arms for the 3 AED groups:

Table Adjusted Steady-State Geometric LS Mean Ratio and 90% CI of Dose Normalized Lamotrigine Steady State PK Parameters XR vs. IR

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
Cτ/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

- The steady-state mean trough concentrations for Lamotrigine XR were equivalent to or higher than those of lamotrigine IR depending on concomitant AED.
- A mean reduction in the lamotrigine Cmax by 11-29% was observed for lamotrigine XR compared to lamotrigine IR resulting in a decrease in the peak to trough fluctuation in serum lamotrigine concentrations.

- The fluctuation index was reduced by 17% in patients taking enzyme-inducing AED, 34% in patients taking VPA and 37% in patients taking neutral AEDs.
- Lamotrigine XR and lamotrigine IR regimens were almost similar (6% decrease) with respect to mean AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR.

However, in these groups there were some individuals that had a greater reduction in Cmax and AUC upon conversion to LAMICTAL XR at steady state. The percent reduction in these outliers in each of these groups is given in the following Table:

Group	% reduction in AUC(0-24)	% reduction in Cmax
Inducers	57-70% (N=2) 29% (N=1)*	45-77% (N=3)
Neutrals	27% (N=1)*	30% (N=1)*
Inhibitors	70% (N=1)**	70% (N=1)**

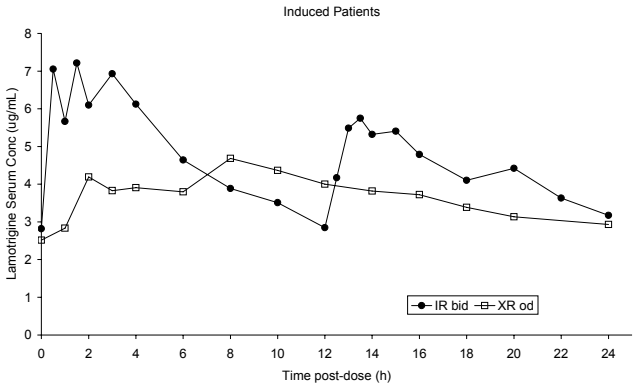
*these are still within the inter-subject variability seen with lamotrigine (i.e. up to 40% variability seen in other studies)

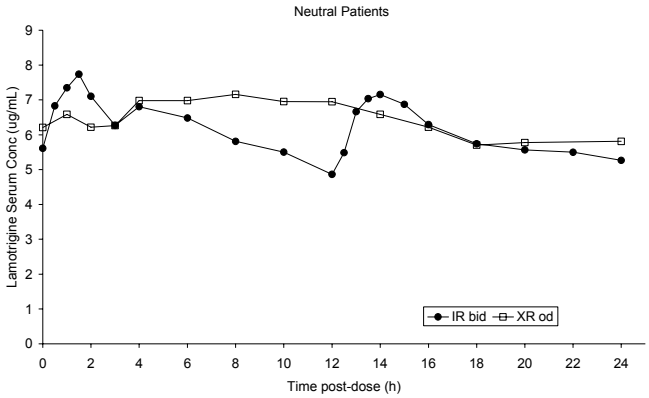
**This subject has a reduction in exposure even on converting back to the IR treatment on Day 29, hence this reduction could be due to some other reason that could not be determined.

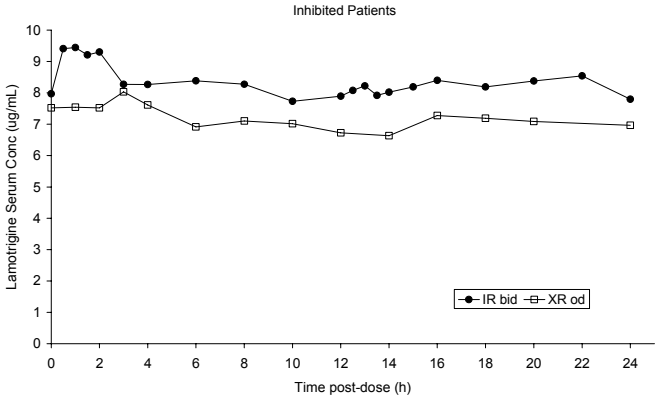
This shows that especially in Inducer Group, some subjects may have much lower levels in the LAMICTAL XR treatment. The therapeutic response in these groups may be different and should be monitored for appropriate dose escalation as needed. For further details on individual data please refer to pages 147-153 of this review.

The plasma concentration time profiles for the IR and XR formulation based on concomitant AED is given below:

Figure **Median Serum Lamotrigine Concentration-Time Profiles for Steady-State IR and Steady State XR for each AED Group**







The following Table shows the comparisons immediately after switching from the IR to the ER dosage form:

Table: Statistical Summary of Serum LTG PK Parameters – Day 15 vs Day 14

Serum LTG PK Parameter	AED Group	Geometric LS Mean Ratio Extended Release (Day 15) / IR (Day 14)	90% CI
AUC(0-24) / Total Daily Dose	Overall	0.87	0.827, 0.908
	Induced	0.82	0.759, 0.896
	Inhibited	0.95	0.874, 1.032
	Neutral	0.83	0.770, 0.897
Cmax / Total Daily Dose	Overall	0.80	0.763, 0.837
	Induced	0.73	0.675, 0.799
	Inhibited	0.92	0.845, 0.993
	Neutral	0.76	0.702, 0.820

- Immediately after the conversion from IR on Day 14 to the extended release formulation on Day 15, a comparable (about 5% reduction) total daily exposure in terms of dose-normalised AUC(0-24) was observed in subjects who were in the inhibiting AED group. For subjects taking inducing and neutral AEDs, a decrease in AUC(0-24) was observed with a mean decrease of 17% in subjects taking neutral AEDs and a mean decrease of 18% in subjects taking enzyme inducing AED.
- There was a reduction in dose normalized mean Cmax in all three AED groups. There was a mean decrease of 8% in Cmax in subjects who were taking inhibiting AEDs, 24% in neutrals and 27% in subjects taking enzyme inducing AEDs.

However, in these groups there were some individuals that had a greater reduction in Cmax and AUC upon conversion to LAMICTAL XR immediately after switching on the following day. The percent reduction in these outliers in each of these groups is given in the following Table:

Group	% reduction in AUC(0-24)	% reduction in Cmax)
Inducers	53% (N=1) 40% (N=2)	41-60% (N=3) 3-fold Increase (N=1)**
Neutrals	27-33%% (N=4)*	32% (N=4)*
Inhibitors	No change	No change

*This is within the intersubject variability ** one subject in the Inducer group had a 3-fold higher Cmax

This shows that some of these subjects in the inducer group may not have the same seizure control immediately upon switching as well as at steady state when on concomitant enzyme inducing antiepileptics and therefore should be monitored.

Based on these observations the sponsor's proposal to switch directly to the equivalent XR dose should also be evaluated by the Medical Officer.

2.2.8 Does LAMICTAL XR prolong QT or QTc interval?

Please refer to the review by the IRT team.

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

Yes, lamotrigine is adequately measured in the plasma. For details of the assay validation, please refer to page 195 of the review.

2.2.10 What are the general ADME characteristics of LAMICTAL XR?

The key ADME characteristics of lamotrigine are derived from the IR formulation. The pharmacokinetic parameters after the administration of LAMICTAL XR are summarized in the following question. Absorption from the ER dosage form is slower as compared to the IR dosage form. Median peak concentrations are reached at 10-14 hours post dose from the ER dosage form compared to about 1-5 hours from the IR dosage form in healthy volunteers. In epilepsy patients, the median time to peak concentration (T_{max}) following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone, 9 to 11 hours in patients taking VPA, and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA.

The distribution, metabolism and elimination characteristics are the same as that of the IR dosage form, with the half-life also being similar with the two dosage forms. The mean half-life was about 37-44 hours in healthy subjects for the XR and about 38 hours for IR dosage form in a crossover study using the 25 mg strength (according the IR label, the mean half-life of the IR dosage form is 33 hours). The half-life of lamotrigine changes depending on the concomitant AED in patients. Although the sponsor has not characterized the half-life of the XR dosage with concomitant AEDs, it is reasonable to expect them to be similar to the IR dosage form.

2.2.11 What are the basic pharmacokinetic parameters of LAMICTAL XR after single and multiple doses?

The single and repeat dose pharmacokinetics of 25 mg lamotrigine extended release tablets were evaluated in LAM10005 using the prototype formulation. The final 25 mg tablet remained relatively unchanged other than a change in the manufacturing process, hence can be used to describe single and repeat dose pharmacokinetics.

There was no to-be marketed formulation that evaluated the single dose parameters of all the strengths in a pharmacokinetic study. Multiple dose pharmacokinetic parameters of all the strengths of the commercial formulation were evaluated in Study LAM 10017. The single and multiple dose pharmacokinetic parameters from these studies is given in the following Table:

Table: Summary Table of Lamotrigine Pharmacokinetics following Single and Repeat Dose (od) of 25 mg Lamotrigine Extended Release (Geometric mean (CVb%)) [Study LAM10005 using prototype formulation]

Parameter	Single Dose (Day 1)	Repeat Dose (Day 14)
AUC(0-∞) (ug·h/mL)	18.1 (41.7%)	N/A
AUC(0-24) (ug·h/mL)	3.74 (24.8%)	14.3 (38.8%)
Cmax (ug/mL)	0.24 (23.1%)	0.67 (36.4%)
tmax[a] (h)	20.0 (10.0, 24.0)	10.0 (3.98, 20.0)
t1/2 (h)	44.1 (39.5%)	39.4 (37.9%)
Fluctuation Index[b]	Not analysed	0.22 (32.6%)

[a] Median (Range)
[b]Fluctuation Index: (Cmax-Cmin)/Cavg
NA – not applicable to report repeat dose AUC(0-inf)

Table: Repeat Dose Pharmacokinetics of Lamotrigine Following Administration of Lamotrigine XR (25, 50, 100 and 200 mg) (Geometric Mean (CVb%) [Study LAM10017 using commercial formulation]

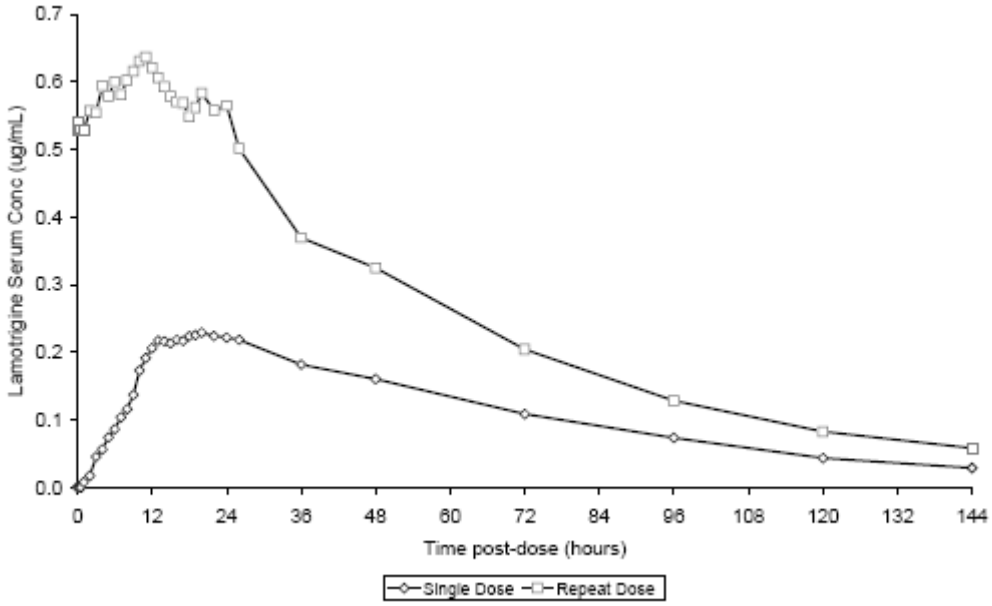
Treatment	N	AUC(0-τ)ss (ug.h/ml)	Cmax (ug/ml)	Tmax (h)	Cτ (ug/ml)	Fluctuation Index
25 mg XR	21	14.5 (24.6)	0.67 (24.3)	14.0 (3-23.9)	0.59 (24.6)	0.13 (0.05-0.20)
50 mg XR	20	23.5 (31.5)	1.08 (31.0)	14.0 (0-23.9)	0.94 (39.4)	0.095 (0.02-0.20)
100 mg XR	19	52.1 (26.9)	2.56 (25.7)	12.0 (0-23.9)	1.93 (31.0)	0.29 (0.07-0.66)
200 mg XR	18	87.4 (26.2)	4.22 (26.9)	10.0 (0.5-23.9)	3.36 (27.3)	0.22 (0.12-0.44)

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

Based on Study LAM 10005 using the 25 mg strength, there was an approximate 3-fold increase in Cmax and AUC(0-24) following repeat dose administration of the 25 mg XR formulation in comparison to single dose. There was evidence of auto-induction as mean terminal phase half-life decreased from 44 h for a single dose to 39.4 h following repeat dosing (although note that the variability is about 40%). This finding is consistent with that observed with lamotrigine IR. The median time to Cmax (tmax) following repeat dosing of lamotrigine XR was 10 h compared to a median tmax of 20 h for a single dose.

The median concentration time profile following single and repeat dosing is shown in the following Figure:

Figure: Median Lamotrigine Plasma Concentration-Time Profiles Following Single and Repeat Dose Administration of Lamotrigine XR (25 mg od).



2.2.13 What is the variability in the PK data?

The within-subject variability of steady-state Cmax and AUC in healthy volunteers was (18-20 %, LAM10017). Between-subject variability following both single and repeat dose for Cmax and AUC in healthy volunteers was ~17-40 %. However, in study LEP 103944 (IR to ER conversion study), between subject variability appeared to be higher (~40-100%). The IR arm in this study also appeared to have high variability. Otherwise in general the variability of 17-40% seen with the XR formulation was consistent with that observed for the IR formulation in previous studies.

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

The steady-state pharmacokinetics of lamotrigine in patients with epilepsy in the "neutral group" in Study LEP103944 were similar to those observed in healthy volunteers (Study LAM10017. A summary of the dose normalized (to a 1 mg dose) Cmax and AUC(0-24) values of lamotrigine in healthy volunteers and patients are provided in the following Table.

Table Comparison of Steady-State Pharmacokinetics of Lamotrigine in Epileptic Patients and in Healthy Volunteers following Administration of Lamotrigine XR (Geometric Mean (CVb%)

Parameter	Healthy Volunteers (N=57)	Patients (N=13)
[a]Cmax (ug/mL)/mg	0.023 (29.0%)	0.020 (28.3 %)
[a]AUC(0-24)ss (ug.h/mL)/mg	0.48 (28.9 %)	0.41 (27.3 %)
CL/F(L/h)	2.11 (28.9 %)	2.46 (27.3 %)
tmax (hr)[b]	10 (0-24)	6.00 (0-24)

[a] Cmax and AUC(0-24)ss values are dose normalised to a 1 mg dose

[b] Median (Range)

The mean dose normalized Cmax and AUC(0-24)ss ranges and associated between-subject variability (CVb%) were similar in healthy volunteers and patients taking lamotrigine as monotherapy or lamotrigine and "neutral" AED therapy.

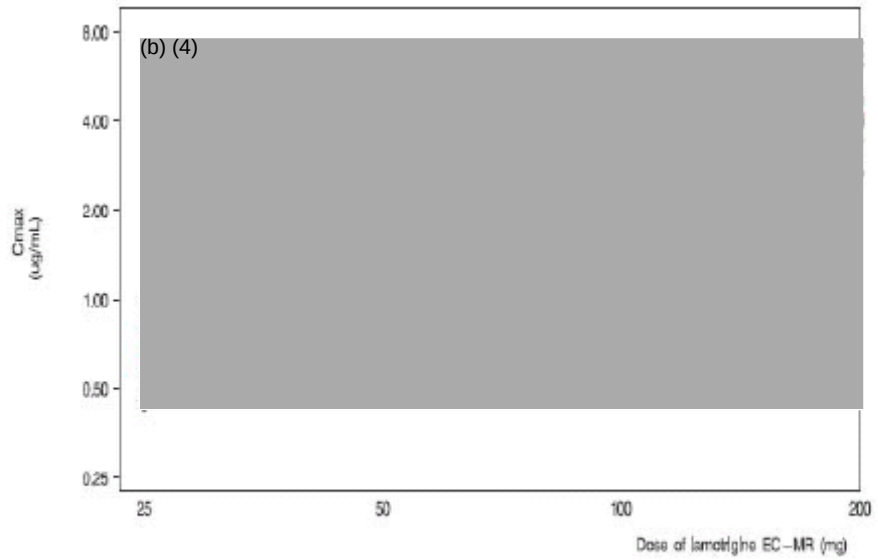
2.2.15 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The increase in systemic exposure to lamotrigine was dose proportional between 50 and 200 mg XR. At doses between 25 mg and 50 mg, the increase in exposure was less than dose proportional, with a 2-fold increase in dose resulting in an approximate 1.6-fold increase in exposure.

The dose-proportionality of lamotrigine XR was evaluated under steady-state conditions in healthy volunteers across the available tablet strength range of 25 – 200 mg (od) in Study LAM10017. Assessment of dose-proportionality was performed using the power model. Dose-proportionality would have been concluded if the 90% confidence intervals of the slope for Cmax and AUC(0-24)ss were within the range of 0.893-1.107. This 90% CI criteria were derived based on the 8-fold dose range of 25-200 mg.

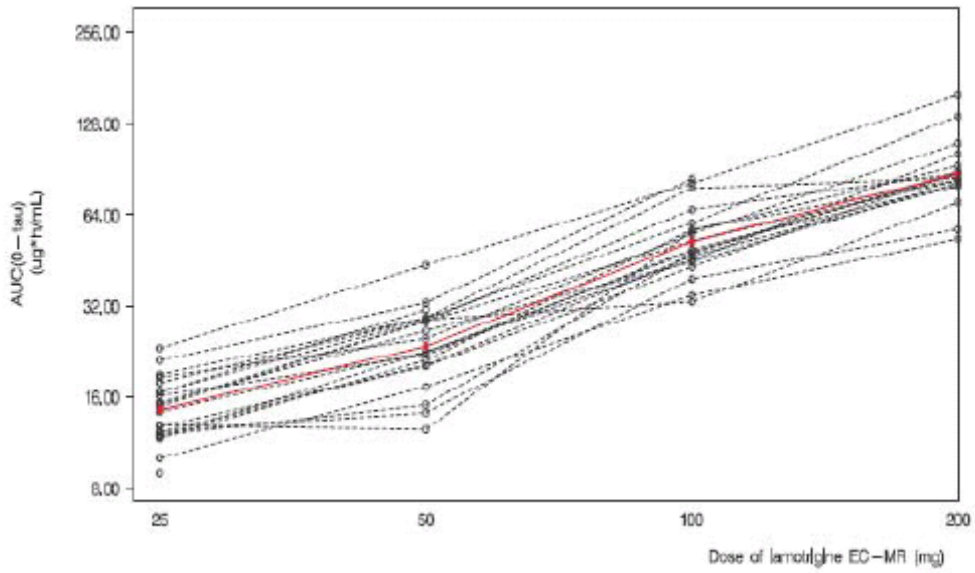
Plots of individual log-transformed Cmax and AUC(0-24)ss values versus dose of lamotrigine XR are presented in the following Figures:

Figure: Individual Steady-State Cmax values (log-transformed) versus Dose of Lamotrigine XR (25, 50, 100 and 200 mg).



Red solid line represents the geometric mean versus dose

Figure: Individual Steady-State AUC(0-24)ss values (log-transformed) versus Dose of Lamotrigine XR (25, 50, 100 and 200 mg)



A summary of the steady-state Cmax and AUC(0-24)ss values for the 25, 50, 100 and 200 mg tablet strengths of lamotrigine XR are presented in the following Table:

Table: Summary of Steady-State Cmax and AUC(0-24)ss for Lamotrigine XR (Geometric Mean (CVb%))

XR Dose	N	Cmax (ug/mL)	AUC(0-24)ss (ug.h/mL)
25mg	21	0.67 (24.3)	14.5 (24.6)
50 mg	20	1.08 (31.0)	23.5 (31.5)
100 mg	19	2.56 (25.7)	52.1(26.9)
200 mg	18	4.22 (26.9)	87.4 (26.2)

A summary of the results of power analysis is given in the following Table:

Table: Summary of Results of Dose Proportionality Assessments for Lamotrigine XR Assessed by Power Model over the Dose range 25-200 mg od

Parameter	Adjusted Mean Slope	Standard Error	90% CI
AUC(0-24)ss	0.897	0.026	(0.853, 0.941)
Cmax	0.928	0.028	(0.881, 0.975)

Assessment of dose proportionality over the dose range 25-200 mg XR using power model, showed a less than proportional increase in AUC (0-24)ss and Cmax with increasing dose. The slope was approximately of 0.9 and the 90% confidence limit lay outside the pre- defined limits of 0.893 – 1.107.

Based on the plots of individual lamotrigine Cmax and AUC(0-24)ss values versus dose, proportionality of lamotrigine over the dose range 50-200 mg was tested. For a four-fold dose range, the pre-defined 90% CI for concluding dose proportionality is 0.8391 – 1.1609.

A summary of the statistical evaluation using the power model for this dose range is presented in the following Table:

Table: Summary of Results of Dose-Proportionality Assessment for Lamotrigine XR Assessed by the Power Model over the Dose range 50 – 200 mg od

Parameter	Adjusted Mean Slope	Standard Error	90% CI
AUC(0-24)ss	0.969	0.045	(0.892, 1.046)
Cmax	1.004	0.054	(0.920, 1.008)

Assessment of dose proportionality of the dose range 50-200 mg showed dose proportionality for both Cmax and AUC(0-24)ss. The slope of the power model was close to unity and the 90% CI was completely contained within the pre-defined range of 0.8391-1.1609.

Therefore, LAMICTAL XR was dose proportional in the dose range of 50-200 mg.

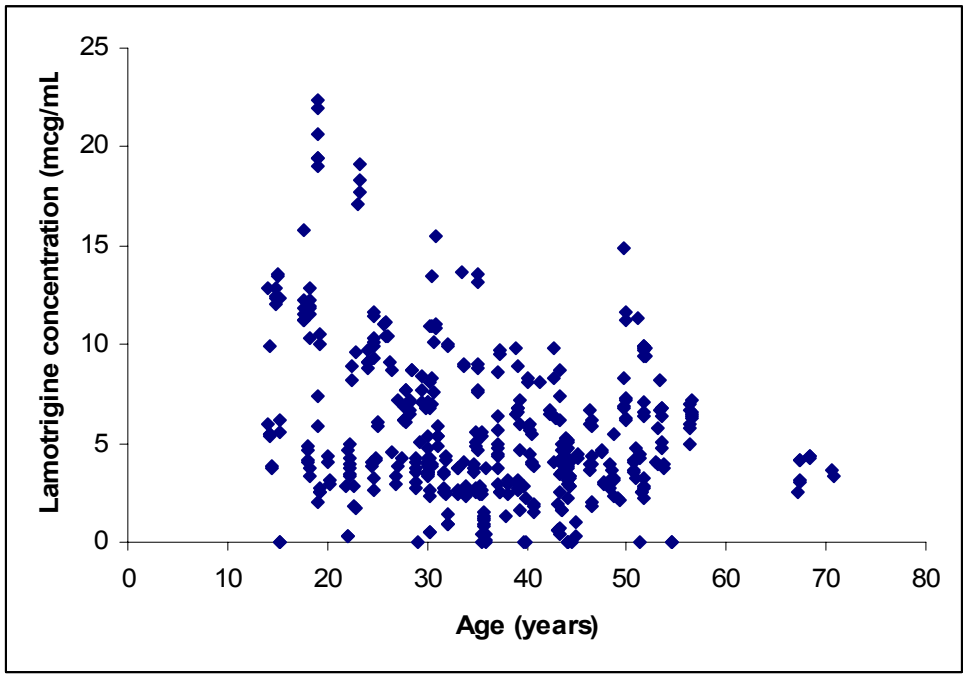
2.3 INTRINSIC FACTORS

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 general intrinsic factors that affect the pharmacokinetics of lamotrigine were evaluated using lamotrigine IR and were provided in the initial NDA (NDA 20-241). Same labeling language is used for the LAMICTAL XR as that approved for the IR dosage form.

In the population analysis of the pivotal clinical study race and age were not significant covariates. However, it is important to note that regarding the effect of age, there were 7 subjects (ages 13-18) on lamotrigine and 9 subjects (ages 13-18) on placebo. The lamotrigine concentrations based on sparse samples (4-6 samples per subject) were similar to that of the adults, as shown in the Figure below:

Figure: Effect of age on lamotrigine plasma concentrations



Although there are few subjects between the age range of 13-18, additional PK study is not necessary because (i) concentrations (and dosing regimen) were similar to the adults and there were at least 4-6 samples per subject on three different visits during the maintenance phase, (ii) dosing in partial seizures for the IR formulation is same for ages 12 and older; (iii) relative bioavailability to the IR formulation in patients is known

(overall 90% relative BA), hence overall the exposures are not expected to be very different and the effectiveness of lamotrigine IR in the age range 12-18 has been established.

2.4 EXTRINSIC FACTORS

The influence of extrinsic factors on the pharmacokinetics of lamotrigine was described in detail in the lamotrigine IR NDA for the treatment of epilepsy and bi-polar disorders (NDA 20-241). No new information has been given in this application. No new drug interaction studies have been conducted with LAMICTAL XR, except with esomeprazole.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Is the proposed to-be-marketed formulation of LAMICTAL XR bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The to-be-marketed formulation was used in the pivotal clinical effectiveness study LAM10034 and the main clinical pharmacology studies LAM10017 and LAM100014 that evaluated dose proportionality of all the strengths of LAMICTAL XR and the food effect, hence a bioequivalence study was not warranted in this case.

2.5.2 What is the relative bioavailability of LAMICTAL XR compared to the IR formulation?

The relative bioavailability of lamotrigine XR was compared to that of lamotrigine IR in both healthy volunteers as well as in patients with epilepsy.

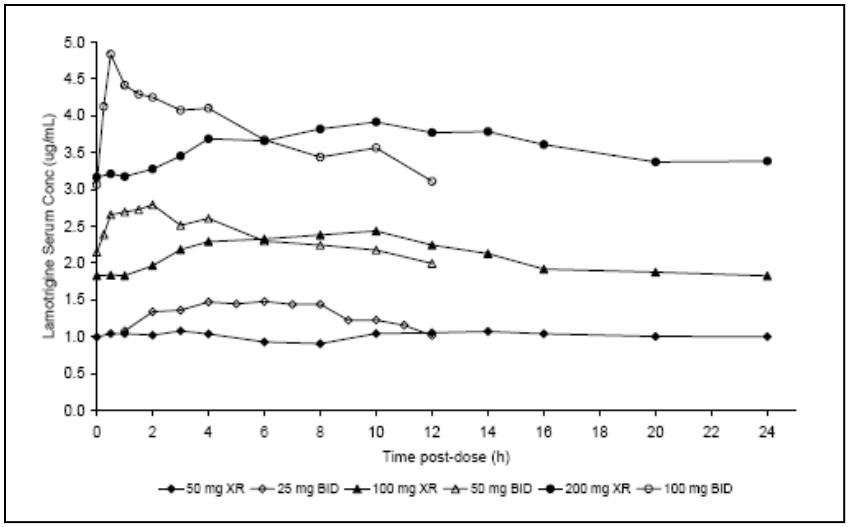
Healthy Volunteers:

In LAM10017, the relative bioavailability of lamotrigine XR was compared to that of lamotrigine IR, at steady-state, in two parallel groups of healthy volunteers. One group of subjects received lamotrigine IR, which was titrated using the standard lamotrigine titration schedule, from 25 mg once a day (o.d) up to 100 mg bid. The other group of subjects received lamotrigine XR, which was titrated using the same total daily dose titration schedule as was used for lamotrigine IR, from a starting dose of 25 mg od up to 200 mg od.

The relative bioavailability of 50 mg XR versus 25 mg bid (IR), 100 mg XR versus 50 mg bid (IR) and 200 mg XR versus 100 mg bid (IR) was evaluated.

The relative bioavailability comparisons were based on direct comparisons of Cmax and Cτ and dose normalized AUC(0-τ)ss.
Median steady-state concentration-time profiles for lamotrigine showed a slower rate of absorption for lamotrigine XR compared to lamotrigine IR and a lower degree of fluctuation in lamotrigine concentrations (see Figure below)

Figure: Median Steady-State Lamotrigine Serum Co-Administration of Lamotrigine XR (50, 100 and 200 mg) and Lamotrigine IR (25, 50 and 100 mg BID)



A summary of PK parameters for lamotrigine following administration of lamotrigine XR(50, 100 and 200 mg) and lamotrigine IR (25, 50 and 100 mg bid) is presented in the following Table:

Table: Pharmacokinetics of Lamotrigine Following Administration of Lamotrigine XR (25, 50, 100 and 200 mg) and lamotrigine IR (25, 50 or 100 mg bid) (Geometric Mean (CVb%)

Treatment	N	AUC(0-τ)ss[a] (ug.h/mL)	Cmax (ug/mL)	Tmax (h)[b]	Fluctuation Index[b,c]
25 mg (XR)	21	14.5 (24.6)	0.67 (24.3)	14.0 (3.00 – 23.9)	0.13 (0.05–0.20)
25 mg b.i.d. (IR)	23	14.4 (27.7)	1.46 (26.4)	1.00 (0.25 – 4.00)	0.35 (0.22–0.63)
50 mg (XR)	20	23.5 (31.5)	1.08 (31.0)	14.0 (0.00 – 23.9)	0.095 (0.02–0.20)
50 mg b.i.d.(IR)	17	26.8 (26.4)	2.87 (21.0)	0.50 (0.25 – 1.50)	0.40 (0.23-0.77)
100 mg (XR)	19	52.1 (26.9)	2.56 (25.7)	12.0 (0.00 – 23.9)	0.29 (0.07–0.66)
100 mg b.i.d (IR)	17	47.9 (27.9)	5.13 (23.1)	0.50 (0.25 – 3.07)	0.42 (0.28–0.72)
200 mg (XR)	18	87.4 (26.2)	4.22(26.9)	10.0 (0.50 – 23.9)	0.22 (0.12–0.44)

[a] τ is the dosing interval i.e. 12 h for the IR formulation and 24 h for the XR formulation
[b] presented as median (range)
[c] Fluctuation Index = (Cmax-Cmin)/Cavg, where Cavg is the average serum concentration =(AUC(0-τ)/τ)

The rate of absorption of lamotrigine following administration of the XR formulation was

slower than for the IR formulation. The median time to Cmax for XR was ~10 – 14 hours compared to 0.5 – 1 hours for the IR formulation. The fluctuation index for the XR formulation (median range of 0.095 to 0.29) was lower than that observed for IR formulation (median range of 0.35 -0.42).
Point estimates and associated 90% CI for the ratios of Cmax, Cτ and dose-normalized AUC(0-τ)ss, for XR relative to IR regimen are presented in the following Table:

Table: Summary Table of Relative Bioavailability Assessment of the Lamotrigine XR versus IR Daily Dose for Cmax, Ctau and Dose Normalised (AUC)ss)

Parameter	Daily Dose (mg)	LS Geo Mean XR	LS Geo Mean IR	Ratio	90% CI
AUC(0-τ)ss (ug.h/mL)/mg[a]	50	0.47	0.58	0.81	(0.71 – 0.94)
	100	0.52	0.54	0.97	(0.83 – 1.13)
	200	0.44	0.48	0.91	(0.78 – 1.06)
Cmax (ug/mL)	50	1.08	1.46	0.74	(0.65 – 0.84)
	100	2.56	2.87	0.89	(0.78 – 1.03)
	200	4.22	5.13	0.82	(0.71 – 0.95)
Cτ (ug/mL)[a]	50	0.94	1.03	0.91	(0.78 – 1.06)
	100	1.93	1.90	1.01	(0.85 – 1.21)
	200	3.36	3.31	1.01	(0.85 – 1.21)
[a.] Dose Normalised AUC(0-τ) where τ is the dosing interval, 24 h for XR and 12 h for IR					

- In terms of dose-normalized AUC(0-τ), the 50 mg, 100 mg and 200 mg EC-MR formulations show a mean relative bioavailability of 81%, 97% and 91%, respectively, compared to the IR formulations at the same daily dose.
- Steady-state trough concentrations for all three doses were close to 100 % in comparison to the IR formulation.
- In terms of Cmax, the maximum concentration of the EC-MR formulation was lower than the IR by approximately 11-26 % across the dose range.

Patients with Epilepsy:

In LEP103944, the pharmacokinetics of lamotrigine was evaluated in patients switching from a stable maintenance dose of lamotrigine IR bid to lamotrigine XR od based on the same daily dose. Pharmacokinetic assessments were conducted at steady-state following administration of lamotrigine IR bid (Day 14), on the first day of switching to the lamotrigine XR formulation od (Day 15), and then at steady-state for the XR formulation od (Day 28). The following day (Day 29), patients were switched back to their lamotrigine IR regimen using the same daily dose, and intense pharmacokinetic sampling was again conducted.

The relative bioavailability of XR and IR was studied based on three categories of concurrent antiepileptic drug(s) (AED) treatment:

- Group 1 (Neutral group): subjects taking LTG IR monotherapy or lamotrigine LTG IR with a non-inducing, non-inhibiting AED.
- Group 2 (Induced group): subjects taking LTG IR and an inducing AED (with or without a neutral AED).
- Group 3 (Inhibited group): subjects taking LTG IR and valproate (with or without a neutral AED).

The rate of absorption of lamotrigine was slower following administration of lamotrigine XR compared to lamotrigine IR. In each of the three groups, the median time to Cmax following administration of lamotrigine IR was between 1 and 1.5 hours post-dose, whereas, following administration of lamotrigine XR, the median time to Cmax was increased to 4 – 6 h post-dose in the induced group, 6 – 10 h post-dose in the neutral group and 9 – 11 h post-dose in the inhibited group. Steady-state Cmax values were ~30% lower in the induced group and ~10% lower in the neutral and inhibited groups following administration of XR, compared to IR.

An assessment of the relative bioavailability of steady-state lamotrigine XR compared to lamotrigine IR (Day 28 vs. Day 14) was conducted using analysis of variance and is presented in the following Table:

Table Adjusted Steady-State Geometric LS Mean Ratio and 90% CI of Dose Normalized Lamotrigine Steady-State PK Parameters XR vs. IR

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
$C\tau$/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

- The overall relative bioavailability based on dose normalized AUC(0-24) following conversion from IR to extended-release at steady-state was estimated to be 90%
    - For patients taking the induced AED, however, lower extent of LTG systemic exposure (21% lower AUC and 29% lower Cmax) was observed with the extended-release (estimated ratio for

AUC(0-24): 0.79 (90% CI: 0.688-0.899), and for Cmax: 0.71 (90% CI: 0.614-0.822)) than the IR reference formulation.

- For patients taking neutral AED, extent of differences between the extended-release and IR formulations extent of LTG systemic exposure were minimal

- For patients taking the inhibited AED, extent of differences between the extended-release and IR formulations extent of LTG systemic exposure were also minimal

- In all three AED groups, similar or higher steady-state trough concentrations were observed on attainment of steady-state for the extended-release (Day 28) in comparison to the IR (Day 14).

Lamotrigine XR resulted in fewer fluctuations in lamotrigine concentrations over a 24-hour interval, compared to administration of lamotrigine IR. The reduction in the degree of fluctuation was most marked for the inducers, followed by neutrals and then the inhibited group.

Summary statistics of the derived steady-state serum lamotrigine PK parameters, separated by AED group are presented in the following Table:

Table Steady-State Lamotrigine Pharmacokinetic Parameters (Geometric Mean (CVb%))

	Day	N	AUC(0-24) (ug.h/mL)	Cmax (ug/mL)	Cmin (ug/mL)	FI[a]	Tmax (h)[b]
Induced							
IR	14	12	100 (85.9%)	6.71 (80.5%)	2.66 (100%)	0.99 (40.1%)	1.01 (0.5–2.98)
XR	28	12	79.0 (100%)	4.77 (85.9%)	2.10 (131%)	0.82 (50.0%)	4.00 (0.00–24.0)
Neutral							
IR	14	14	142 (43.4%)	7.82 (39.3%)	4.57 (46.6%)	0.55 (29.5%)	1.50 (0.5–3.02)
XR	28	13	138 (40.8%)	6.83 (38.6%)	4.87 (41.0%)	0.34 (40.6%)	6.00 (0.00–24.0)
Inhibited							
IR	14	12	208 (59.7%)	10.2 (57.5%)	7.43 (53.9%)	0.32 (27.0%)	1.00 (0.50–6.13)
XR	28	10	167 (48.1%)	7.77 (49.0%)	6.31 (47.1%)	0.21 (16.4%)	11.0 (0.00–24.0)

[a] FI = Fluctuation Index = (Cmax-Cmin)/Cavg
[b] presented as median (range)

2.5.3 Are the dosage strengths of LAMICTAL XR equivalent?

Dose strength equivalence has been demonstrated at doses of 50, 100 and 200 mg when lamotrigine XR was administered as 2 tablets or as a single tablet using all four tablet strengths.

The dose strength equivalence of administering 2 lamotrigine XR tablets versus a single lamotrigine XR tablet was studied at steady state at doses of:

- 2x25mg EC-MR tablet vs. 1x50mg EC-MR tablet
- 2x50mg EC-MR tablet vs. 1x100 mg EC-MR tablet
- 2x100mg EC-MR tablet vs. 1x200mg EC-MR tablet

The study (LAM100017) was conducted in healthy volunteers using the currently recommended titration schedule.

Point estimates and associated 90% CI for the ratios of AUC(0-24)ss and Cmax for the dose strength equivalence comparisons of 2 x lamotrigine XR tablets versus 1 x lamotrigine tablet are presented in the following Table:

Table Point Estimates and 90% CI for the Dosage Strength Equivalence of XR once daily formulation

Parameter	Comparison	LS Geo. Mean (Test)	LS Geo. Mean (Ref)	Ratio	90 % CI
AUC(0-24)ss	2x25mg : 1x50mg	26.1	23.5	1.11	(1.01 – 1.23)
Cmax		1.20	1.08	1.11	(1.00 – 1.23)
AUC(0-24)ss	2x50mg : 1x100mg	50.3	52.6	0.957	(0.87 – 1.06)
Cmax		2.43	2.58	0.943	(0.85 – 1.05)
AUC(0-24)ss	2x100mg : 1x200mg	91.9	89.9	1.02	(0.93 – 1.13)
Cmax		4.61	4.33	1.07	(0.96 – 1.19)
Test= two tablets, Reference =single tablet					

Both the 90% CI for AUC and Cmax were completely contained within the pre-defined equivalence range of 0.8 – 1.25, demonstrating dosage strength equivalence.

2.5.4 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 LAMICTAL XR in relation to meals or meal types?

In LAM10014, the effect of food on the highest tablet strength of lamotrigine XR (200 mg) was evaluated. The study was a parallel group study conducted in healthy volunteers, with each subject receiving one single dose of lamotrigine.

Analysis of variance of the effect of food on lamotrigine AUC(0-∞) and Cmax are presented in the following Table:

Table Summary of Point Estimates and 90% Confidence Intervals for Cmax and AUC(0-inf) for the Comparison of XR (200 mg Fed) versus XR (200 mg Fasted)

Parameter	Comparison	LS Gmean (Fed)	LS Gmean (Fasted)	Ratio	90% CI
AUC(0-∞)	Fed:Fasted	122	119	1.03	(0.92,1.14)
Cmax	Fed:Fasted	2.20	1.98	1.11	(1.04,1.19)
LS=least squares model estimate, Gmean=geometric mean; CI=confidence interval					

For both AUC(0-∞) and Cmax, the 90 % confidence interval of the ratio Fed : Fasted for 200 mg XR lay completely within the equivalence range 0.8 – 1.25 indicating a lack of food effect on AUC (0-∞) and Cmax of lamotrigine.

Summary statistics of derived serum lamotrigine PK parameters are presented in the following Table:

Table Summary of Lamotrigine Pharmacokinetic Parameters following administration of Lamotrigine XR (200 mg) in the Fed and Fasted State (Geometric Mean (CVb%))

Regimen	N	Cmax (ug/mL)	AUC(0-∞) (ug.h/mL)	tmax[a] (h)	Tlag[a] (h)	t1/2 (h)
Fasted	46	1.98 (17.5%)	119 (31.0%)	22.0 (7.0 - 36.0)	0.25 (0.0 – 0.50)	32.1 (30.1)
Fed	48	2.20 (21.4%)	122 (33.5%)	16.5 (9.0 – 36.0)	0.50 (0.0 - 2.03)	33.0 (25.1)
[a] Median (range)						

Median tmax values indicate a slightly more rapid attainment of Cmax when lamotrigine was administered with a high-fat meal, compared to the fasted state. But the plasma concentration time profile is flat over the dosing interval that these differences may not be meaningful.

In the clinical trials, lamotrigine XR was dosed without regards to food and this is the proposed dosing recommendation.

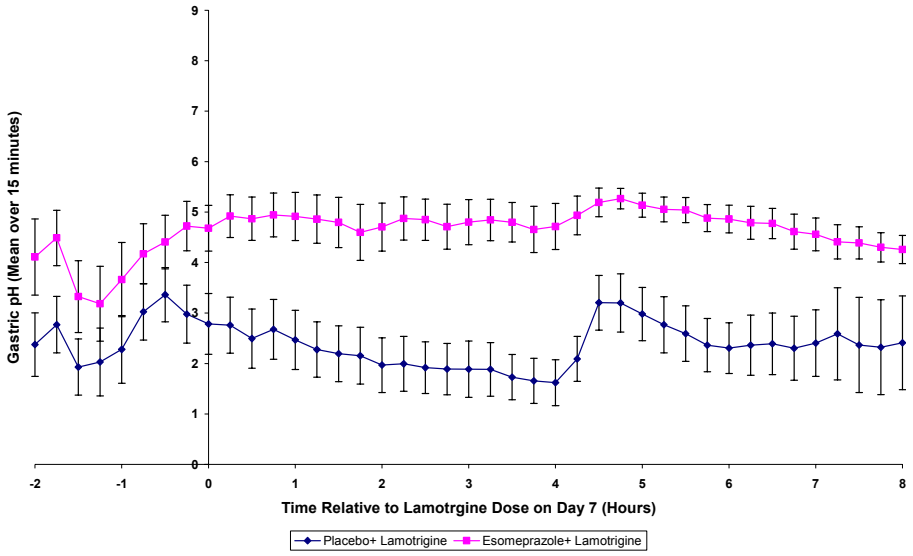
2.5.5 What is the effect of pH on the release rate and oral bioavailability?

The rate of absorption (Tmax) is faster (40%), the extent of absorption is decreased (12%) with no effect on Cmax when lamotrigine XR is administered in a chronically increased gastric pH environment.

In LAM102611, the effect of increased gastric pH of the release characteristics and oral bioavailability of lamotrigine XR (200mg) was evaluated in healthy volunteers. Subjects were dosed with either esomeprazole (40 mg) or placebo daily for 12 days, with concomitant administration of lamotrigine 200 mg XR on day 7.

Gastric pH was measured in each individual from 2 h prior to lamotrigine administration on day 7 until 8 hours post-dose. A summary plot of mean and 95% CI for mean gastric pH versus time, separated by treatment group is presented in the following Figure, and shows a relatively constant pH level in the group receiving esomeprazole in comparison to the group receiving placebo.

Figure Summary Plot of Mean and 95 %CI of Mean Gastric pH versus Time, Separated by Treatment Group



A summary (geometric mean (CVb%)) of the PK parameters following administration of 200 mg of lamotrigine XR in the presence and absence of esomeprazole are presented in the following Table:

Table Summary of PK Parameters for 200mg of Lamotrigine XR in the Presence or Absence of Esomeprazole (Geometric Mean (CVb%))

Parameter	Lamotrigine+Esomeprazole	Lamotrigine+Placebo
AUC(0-∞) (ug.h/mL)	90.7 (26.2)[b]	102.6 (32.9)
Cmax (ug/mL)	1.85 (22.8)	1.89 (23.0)
Tmax (h)[a]	12.0 (6.00 – 24.1)	20.0 (10.0 -24.1)
T1/2 (h)	29.5 (27.2)	30.1 (22.1)
N	31	30
[a] Median (Range) [b] N=30		

Point estimates and associated 90% CI for the ratios of AUC (0-∞) and Cmax for the 200 mg lamotrigine XR with and without esomeprazole (40 mg) are presented in the following Table:

Table Point Estimates and 90% CI for the Bioavailability of 200 mg Lamotrigine XR in the Presence or Absence of Esomeprazole (40 mg)

Parameter	Regimens	Ratio	90% CI
AUC(0-∞)	Esomeprazole : Placebo	0.88	(0.78, 1.00)
Cmax	Esomeprazole : Placebo	0.98	(0.89, 1.08)

The median time to tmax was shorter when lamotrigine XR was administered with esomeprazole (~12 h) compared to administration of lamotrigine alone (~20 h). However, Cmax ranges was similar for the two regimens based on point estimates being close to unity (0.98) and the 90% CI (0.89, 1.08) being within the range associated with equivalence. The overall exposure to lamotrigine (AUC(0-∞)) was slightly lower (~12%) when lamotrigine XR was co-administered with esomeprazole.

This indicates that rate of absorption is faster and the extent of absorption is decreased when lamotrigine XR is administered in a chronically increased gastric pH environment.

2.5.6 Was an IVIVC established for this product?

A validated IVIVC is not yet established due to only 2 release rates and lack of external validation. (b) (4)

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(b) (4)

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

HPLC/MS/MS was used to assess plasma concentrations of lamotrigine. The assay validation was adequate.

Table: Summary Table of Validation Study Parameters

	Full Validation	Abbreviated Validation
Studies supported	LAM10014	LAM10017, LAM102611, LEP103944, LAM100034, SCA104648
Analyte	Lamotrigine (GI267119)	Lamotrigine (GI267119)
Matrix	Human Serum	Human Serum
Method	LC/MS/MS	LC/MS/MS
LLOQ	4 ng/mL	4 ng/mL
Linear range	4 to 4000 ng/mL	4 to 4000 ng/mL
QC samples	4.00, 15.0, 350, 3500, 4000 ng/mL	4.00, 15.0, 350, 3500, 4000 ng/mL
Inter-day precision (from QCs)	%CV ≤ 2.6%	N/AP
Accuracy and intra-day precision (from QCs)	0.1% ≤ %bias ≤ 9.7% %CV ≤ 11.3%	0.9% ≤ %bias ≤ 6.2% %CV ≤ 5.7%
Freeze-thaw stability	At least 3 cycles at -30°C	
Bench top Stability at RT	At least 24 hours at room temperature	
Long term at -30° C	At least 220 days	
Stock Solution Stability	At least 195 days at 4°C	
Recovery Low Med High	Not determined. Absolute recovery determination is not a GSK validation requirement. Generic protein precipitation extraction using (b) (4) is believed to ensure high recovery and good reproducibility. In addition, the method was sufficiently sensitive at the LLOQ with consistent accuracy and precision over the validated calibration range.	

3.0 DETAILED LABELING RECOMMENDATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LAMICTAL XR safely and effectively. See full prescribing information for LAMICTAL XR.

LAMICTAL XR (lamotrigine) Extended-Release Tablets
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES

See full prescribing information for complete boxed warning.

Cases of life-threatening serious rashes, including Stevens-Johnson syndrome, toxic-epidermal necrolysis, and/or rash-related death, have been reported with the use of lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include (5.1):

- **coadministration with valproate**
- **exceeding recommended initial dose of LAMICTAL XR**
- **exceeding recommended dose escalation of LAMICTAL XR**

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4.0 APPENDIX I

4.1 INDIVIDUAL STUDY REVIEW

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LAM10007: An open, randomized, study to investigate the gastrointestinal absorption (of 50 mg single doses) of lamotrigine from small bowel and ascending colon in healthy, male volunteers

Rationale:

This study investigated the regional gastrointestinal absorption of lamotrigine to evaluate **the feasibility of developing a controlled release formulation**. The study was performed using an Enterion capsule, to evaluate the rate and extent of absorption of lamotrigine administered as a powder or solution into the proximal small bowel, distal small bowel and the ascending colon, compared to administration of the IR formulation.

Objectives:

Primary: To evaluate the relative bioavailability of two formulations (powder and solution) of lamotrigine from three sites in the gastrointestinal tract compared to reference to ascertain sites of gastrointestinal absorption

Secondary: To evaluate the relative bioavailability of powder compared to solution of lamotrigine from two sites in the gastrointestinal tract (distal small bowel and ascending colon). To evaluate the relative bioavailability of lamotrigine across sites in the gastrointestinal tract.

The study design is as follows:

Study centre: (b) (4) NG11 6JS.
Methodology: This was a four-way, open-label, randomized, incomplete block design study. The volunteers had to take part in four study days, in addition to a pre-study and post-study visit. Each volunteer received the reference formulation (formulation F: 50 mg of lamotrigine administered as two immediate release (IR) tablets) and three (out of a possible five) test formulations. The test formulations were as follows:- A: 50 mg of lamotrigine powder delivered to the proximal small bowel via the Enterion™ capsule B: 50 mg of lamotrigine powder delivered to the distal small bowel via the Enterion™ capsule C: 50 mg of lamotrigine solution delivered to the distal small bowel via the Enterion™ capsule D: 50 mg of lamotrigine powder delivered to the ascending colon via the Enterion™ capsule E: 50 mg of lamotrigine solution delivered to the ascending colon via the Enterion™capsule

There was a 14-day wash-out period between each study day.

Pharmacokinetic Assessments:

Samples were taken predose and preactivation (Regimens A-E only) and at the nominal times of 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours postactivation/ dosing.
Serum samples were assayed for lamotrigine using a method based upon solid phase extraction followed by LC/MS/MS employing positive-ion Turbo IonSpray ionization (lower limit of quantification (LLQ) 4.00 ng/mL for a 200 uL aliquot of human serum).

Number of subjects:

15 healthy male volunteers, mean age 43 ± 5.2 were planned in order to obtain evaluable data from twelve subjects. Fifteen subjects were given study medication and included in the analysis. Race: White 80%, Black 13%, Other 7%

Treatment administration:

Fifty milligrams of lamotrigine were dosed orally via the Enterion™ capsule either as a solution or as a powder (batch number 479302A). The solution was 59 mg/mL in concentration, with 0.85 mL being added to the capsule. Lamotrigine (50 mg) was also taken orally as the immediate release tablet (reference formulation – batch number WNT543001).

Subjects were fasted from midnight until approximately 07:00. The subjects were then provided with a light breakfast before being administered the study drug at approximately 11.00. The reference formulation was administered with 250 mL water, and the test formulations were taken with 220 mL water followed by a radiolabelled drink containing 4 MBq ^{99m}Tc-DTPA in 30 mL water. This water soluble marker mixed with the water and taken immediately after the capsule provided visual confirmation of the subject's gastrointestinal anatomy and facilitated assessment of the capsule's location as it moved down the upper intestine.

All the capsules administered incorporated an ^{111}In marker (1 MBq) and transit of the capsule was monitored via gamma scintigraphy. Following administration of the test formulations, images were recorded at approximately 10 minute intervals until four hours post-activation and then every 20 minutes until eight hours post-activation. Thereafter images were acquired at 10, 12, 16 and 24 hours post-activation or until the capsule was defecated.

Criteria for evaluation:

Pharmacokinetic parameters determined by non-compartmental methodology included Cmax, Tmax, AUC(0-t), AUC(0-inf), and T1/2. Pharmacokinetic parameters were summarized descriptively for each treatment.

Pharmacokinetic Results:

Pharmacokinetic parameters for lamotrigine following administration of 50 mg lamotrigine as powder or solution formulations using an Enterion™ capsule to three sites in the gastrointestinal tract and from oral administration of the IR tablet are given in the following Table:

Table: Mean (SD) lamotrigine pharmacokinetic parameters by site of activation

	Site of Activation					
Parameter	A	B	C	D	E	F
N	7	9	9	8	7	14
Tmax*	2.00	4.05	0.50	14.00	8.00	1.25
(h)	(0.50-24.00)	(1.00-24.00)	(0.25-4.00)	(6.00-24.00)	(3.00-10.00)	(0.50-4.00)
Cmax	523	496	639	396	426	674
(ng/mL)	(72)	(125)	(271)	(80)	(65)	(128)
AUC(0-t)	28840	27294	19959	22735	24702	27057
(ng.h/mL)	(8015)	(10035)	(7580)	(4435)	(8886)	(8597)
N**	5	5	8	7	5	10
AUC(0-inf)	28297	22728	19128	25333	22480	24729
(ng.h/mL)	(6039)	(6396)	(5751)	(6006)	(7014)	(6035)
T1/2	36.4	31.0	27.7	32.6	31.1	31.6
(h)	(5.5)	(4.2)	(5.1)	(5.2)	(7.1)	(7.1)

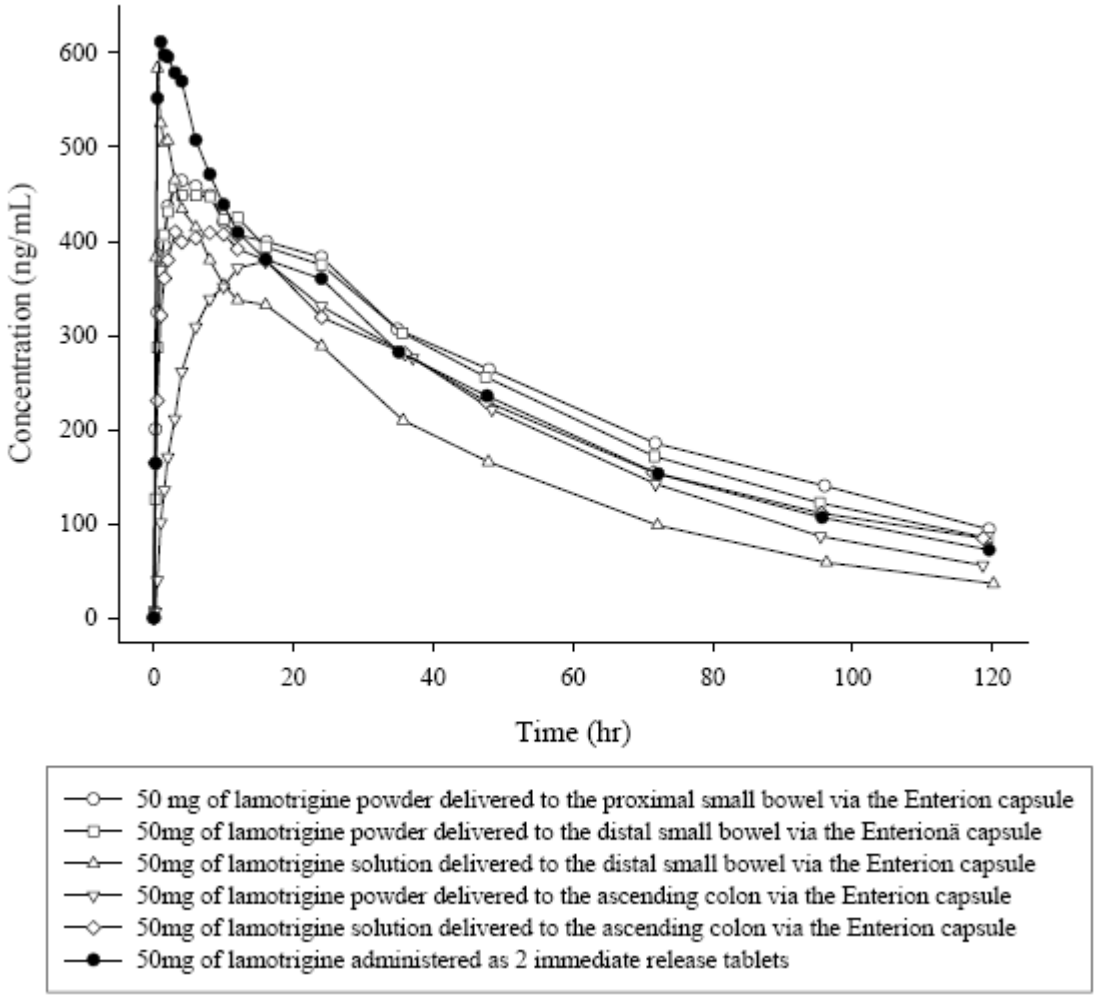
A: 50mg lamotrigine powder, proximal small bowel, Enterion capsule
B: 50mg lamotrigine powder, distal small bowel, Enterion capsule
C: 50mg lamotrigine solution, distal small bowel, Enterion capsule
D: 50mg lamotrigine powder, ascending colon, Enterion capsule
E: 50mg lamotrigine solution, ascending colon, Enterion capsule
F: 50mg lamotrigine as 2 IR tablets
* Median (range)
**T1/2 and subsequently AUC(0-inf) could not be determined in some subjects.

- **Tmax:** Following administration of 50 mg lamotrigine as powder or solution using an Enterion™ capsule delivered to three different sites in the gastrointestinal tract, or as the oral IR tablet, maximal lamotrigine concentrations were achieved fastest with lamotrigine solution delivered to the distal small bowel, and slowest for lamotrigine powder delivered to the ascending colon. Thus, it appears that rate of lamotrigine absorption may be slower when released at GI sites other than the stomach (as a tablet or powder).
- **Cmax:** Lamotrigine Cmax was highest with the IR tablets, although activation of lamotrigine solution delivered to the distal small bowel resulted in a similar Cmax. The lowest Cmax was observed with the lamotrigine delivered to the ascending colon.
- **AUC:** The highest observed AUC(0-t) was for lamotrigine powder delivered to the proximal small bowel, although both lamotrigine powder delivered to the distal small bowel and the IR tablets resulted in similar values. The lowest

observed AUC(0-t) was for lamotrigine solution delivered to the distal small bowel.

- **T1/2:** No major differences were observed in lamotrigine elimination half-life across all regimens.

Figure: Mean lamotrigine serum concentration-time profiles following 50mg of lamotrigine administered as a powder or solution to various sites of the GI tract



The observation of substantially lower serum lamotrigine concentrations was observed in one subject (subject number 00012) receiving Regimen C (solution in the distal small bowel), causing him to be an outlier for that regimen. The reason for this could not be ascertained by the sponsor. Incomplete activation of the capsule, rapid small bowel or colonic transit times and other obvious study conduct-related factors were all excluded as possible causes of this finding. According to the sponsor, this outlier observation is more likely to be artifactual in nature, rather than a result of intrasubject variability in GI absorption of lamotrigine, as the relative magnitudinal difference in this subject's

systemic exposure (relative to the subject's other data) was far in excess of that observed for any other subject in the study.

Primary comparisons of interest: In order to assess the relative bioavailability of lamotrigine from powder and solution formulations delivered to three sites in the gastrointestinal tract compared to that after oral administration of the standard IR tablet, point estimates and 95% confidence intervals were derived for Cmax and AUC for each of the test regimens (A to E) compared back to the IR tablet (F). No adjustments were made for the multiple comparisons.

Table: Point Estimates and 95% Confidence Intervals for the Ratios of the Primary Comparisons of Interest

		Including all subjects		Excluding outlier*	
Parameter	Comparison	Ratio	95% C.I.	Ratio	95% C.I.
AUC(0-inf)	A:F	1.03	(0.79, 1.34)	1.03	(0.90, 1.19)
(ng.h/mL)	B:F	0.95	(0.73, 1.24)	0.88	(0.77, 1.02)
	C:F	0.79	(0.64, 0.98)	0.92	(0.82, 1.04)
	D:F	0.98	(0.77, 1.24)	0.92	(0.81, 1.04)
	E:F	0.91	(0.70, 1.18)	0.94	(0.82, 1.08)
Cmax	A:F	0.77	(0.60, 0.99)	0.79	(0.68, 0.92)
(ng/mL)	B:F	0.74	(0.59, 0.93)	0.73	(0.64, 0.84)
	C:F	0.90	(0.72, 1.12)	1.05	(0.91, 1.21)
	D:F	0.58	(0.46, 0.73)	0.56	(0.48, 0.65)
	E:F	0.62	(0.49, 0.79)	0.64	(0.55, 0.74)

A: 50mg lamotrigine powder, proximal small bowel, Enterion capsule
B: 50mg lamotrigine powder, distal small bowel, Enterion capsule
C: 50mg lamotrigine solution, distal small bowel, Enterion capsule
D: 50mg lamotrigine powder, ascending colon, Enterion capsule
E: 50mg lamotrigine solution, ascending colon, Enterion capsule
F: 50mg lamotrigine as 2 IR tablets
* Residual and normal probability plots revealed Subject 00012, Regimen C to be an outlier, since the AUC and Cmax values were considerably lower than for any other subject

Generally, lamotrigine Cmax and AUC(0-inf) were lower, on average, at the sites of capsule activation compared to the IR tablet, except for lamotrigine powder AUC(0-inf) activated in the proximal small bowel and powder Cmax when administered to the distal small bowel.

Other comparisons of interest: In order to evaluate the relative bioavailability of lamotrigine from powder and solution formulations delivered to two sites in the gastrointestinal tract, point estimates and 95% confidence intervals were derived for Cmax and AUC for the powder formulation compared to solution in the distal small bowel (B:C) and in the colon (D:E).

Table: Point Estimates and 95% Confidence Intervals for the Ratios of Lamotrigine Administered as Powder Compared to Solution

		Including all subjects		Excluding outlier*	
Parameter	Comparison	Ratio	95% C.I.	Ratio	95% C.I.
AUC(0-inf)	B:C	1.20	(0.91, 1.58)	0.96	(0.82, 1.12)
(ng.h/mL)	D:E	1.07	(0.81, 1.43)	0.98	(0.84, 1.14)
Cmax	B:C	0.83	(0.64, 1.06)	0.70	(0.59, 0.82)
(ng/mL)	D:E	0.93	(0.70, 1.23)	0.88	(0.73, 1.05)

B: 50mg lamotrigine powder, distal small bowel, Enterion capsule
C: 50mg lamotrigine solution, distal small bowel, Enterion capsule
D: 50mg lamotrigine powder, ascending colon, Enterion capsule
E: 50mg lamotrigine solution, ascending colon, Enterion capsule
* Residual and normal probability plots revealed Subject 00012, Regimen C to be an outlier, since the AUC and Cmax values were considerably lower than for any other subject

Lamotrigine AUC(0-inf) was higher, on average, for powder compared to solution in both the distal small bowel and the ascending colon. Cmax was lower for powder compared to solution in the distal small bowel and ascending colon.

In order to evaluate the relative bioavailability of lamotrigine across sites in the gastrointestinal tract, point estimates and 95% confidence intervals were derived for Cmax and AUC for the distal small bowel and colon compared to the proximal small bowel, when lamotrigine was delivered as powder formulations (B:A and D:A).

Table: Point Estimates and 95% Confidence Intervals for Ratios to Assess Bioavailability Across Sites

		Including all subjects		Excluding outlier*	
Parameter	Comparison	Ratio	95% C.I.	Ratio	95% C.I.
AUC(0-inf)	B:A	0.92	(0.67, 1.27)	0.85	(0.72, 1.02)
(ng.h/mL)	D:A	0.95	(0.71, 1.27)	0.89	(0.76, 1.04)
Cmax	B:A	0.96	(0.74, 1.26)	0.92	(0.78, 1.10)
(ng/mL)	D:A	0.75	(0.57, 0.98)	0.71	(0.60, 0.84)

A: 50mg lamotrigine powder, proximal small bowel, Enterion capsule
B: 50mg lamotrigine powder, distal small bowel, Enterion capsule
D: 50mg lamotrigine powder, ascending colon, Enterion capsule
* Residual and normal probability plots revealed Subject 00012, Regimen C to be an outlier, since the AUC and Cmax values were considerably lower than for any other subject

Lamotrigine administered as a powder, resulted in slightly lower Cmax and AUC(0-inf), on average, for the distal small bowel and ascending colon compared to the proximal

small bowel.

Conclusions:

- Systemic exposure to lamotrigine following administration of lamotrigine powder or solution into the proximal small bowel, distal small bowel and the ascending colon suggest that lamotrigine is well absorbed in these areas of the gastrointestinal tract, in terms of AUC(0-inf), similarly to the standard IR tablet.
- Results from this study indicated that a controlled release product for lamotrigine was feasible due to the maintained absorption throughout the length of the gastrointestinal tract.
- Following drug release at various GI sites, the overall extent of lamotrigine absorption (relative to the IR tablet) appeared to be highest in the proximal small bowel and was comparable between the distal small bowel and ascending colon, either as powder or solution.
- Except for release of solution in the distal small bowel, lamotrigine release at the other GI sites resulted in notably lower Cmax values, compared with those observed after oral administration of the IR tablet, with an accompanying delay in times to maximal serum concentrations. The delay in Tmax was greatest for the ascending colon.

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LAM100014: An open-label study to demonstrate lack of effect of food on the pharmacokinetics of 200 mg lamotrigine enteric coated modified release tablets in healthy male and female volunteers.

Objectives:

Primary: To demonstrate lack of effect of food on the pharmacokinetics of 200 mg lamotrigine EC modified release in healthy male and female volunteers.

Secondary: To evaluate the tolerability of single doses of 200 mg lamotrigine EC modified release tablets administered under fasted and fed states in healthy male and female volunteers.

The study design is as follows:

Study center: (b) (4)	CB3 7TR

Methodology:
This was an open-label, parallel group study in 95 healthy young male and female subjects. A parallel group design was selected to avoid repeated administration of single doses of lamotrigine to healthy subjects; it was considered that repeated administration of single doses of lamotrigine in excess of 25 mg (rather than using the recommended dose titration schedule) might have increased the risk of skin rash.

The study included a screening evaluation, a single treatment episode for each subject and a follow-up evaluation

Group A: A 200 mg tablet of lamotrigine EC modified release formulation under fasted conditions.

Group B: A 200 mg tablet of lamotrigine EC modified release formulation under fed conditions.
Subjects randomised to Group B received their dose of study medication following a 'FDA' standard breakfast (consumed over a period of 25 minutes).
Subjects fasted from 22:00h the evening prior to dosing, and received study medication within 10 minutes of completing the breakfast.

Each subject was involved in the study for a total of 10 days (i.e. 1 day for screening visit, 8 days for the PK sampling period and 1 day for the follow-up evaluation) over the course of 5 weeks.

Pharmacokinetic Assessments:
Samples were taken predose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 36, 48, 72, 96, 120 and 144 hours following dosing (32 samples).

Serum samples were assayed for lamotrigine using a method based upon solid phase extraction followed by LC/MS/MS employing positive-ion Turbo Ion Spray ionization (lower limit of quantification (LLQ) 4.00 ng/mL).

Study LAM10014: Serum concentrations of lamotrigine in QC samples			
	Nominal Concentrations		
	QC 1	QC 2	QC 3
	15.00 ng/mL	350.00 ng/mL	3500.00 ng/mL
Overall Mean	15.3	353.0	3644.6
S.D.(within run means)	1.0	21.4	187.6
Precision(%CV)	6.5	6.1	5.1
Average Bias %	1.6	0.9	4.1
N	95	96	96
Average Within Run Precision (%)	5.8	2.9	2.8
Between Run Precision (%)	0.4	0.8	0.6

Number of subjects:
Ninety five (95) volunteers entered the study and 94 completed (51 males and 43 females). One subject withdrew from the study (subject number 73, male) and was subsequently replaced.

Treatment administration:
Lamotrigine was supplied as 200 mg EC modified release tablets (batch number 4ZM3860), given as a single dose.

Criteria for evaluation:
The primary endpoints were Cmax and AUC(0-∞) of lamotrigine.
Secondary endpoints were tmax and t1/2 of lamotrigine.
Safety parameters were adverse events (AEs), changes in biochemistry, haematology, urinalysis, electrocardiogram (ECG), blood pressure and heart rate.

Pharmacokinetic Results:

The pharmacokinetic parameters and the mean plasma concentration time profile under fasted and fed conditions is given below:

Table: Summary of Serum Lamotrigine Pharmacokinetic Parameters[1]

Treatment	N	Cmax (ng/mL)	tmax (h)[2]	Tlag (h)[2]	AUC(0-∞) (ng.h/mL)
200 mg lamotrigine EC-MR, Fasted	46	1984 (17.5)	22.0 (7.0 - 36.0)	0.25 (0.0 – 0.50)	118875 (31.0)
200 mg lamotrigine EC-MR, Fed	48	2202 (21.4)	16.5 (9.0 – 36.0)	0.50 (0.0 - 2.03)	122147 (33.5)

The apparent terminal half-life, t1/2, was comparable between the treatments, with a

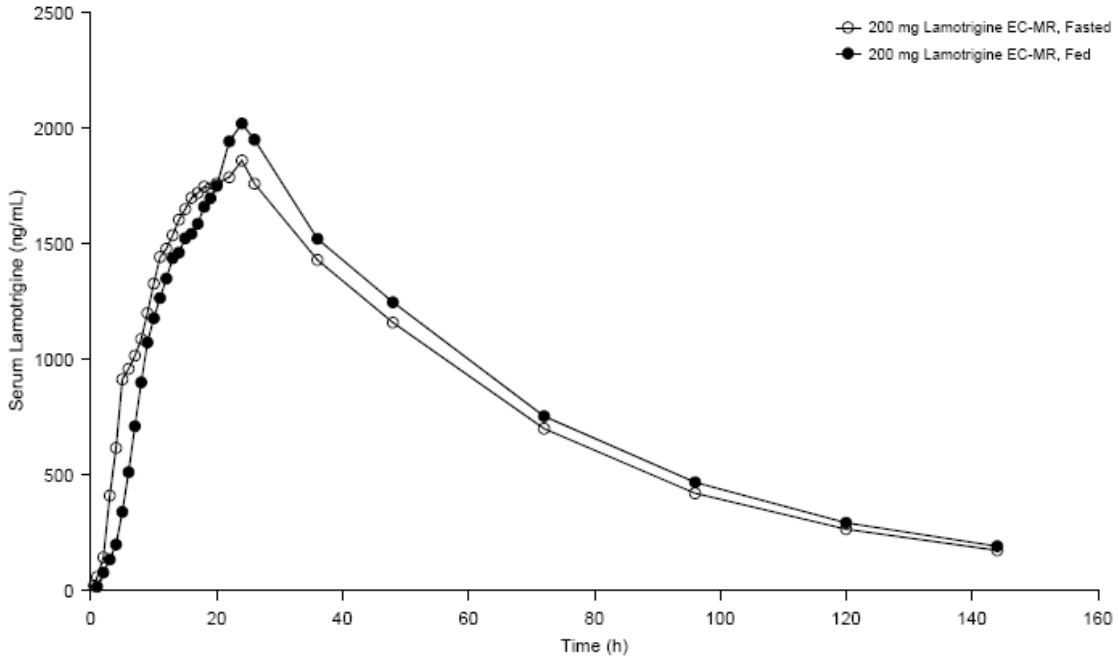
median (range) of 32 (18.0-65.0) hours in the fasted state and 34 (19-55) hours in the fed state.

Although there was a slightly longer lag time in appearance of quantifiable serum concentrations for the fed state, maximal lamotrigine concentrations were achieved, on median, 5.5 hours earlier for the fed relative to the fasted state. The ranges of these tmax values were, however, similar between the regimens.

According to the sponsor, the tendency towards earlier maximal concentrations in the fed state is possibly related to a more rapid dissolution of the EC-MR (DiffCORE™) tablet's enteric coat in an elevated gastric pH produced by a high fat meal intake. The release of lamotrigine from the EC-MR formulation is controlled by means of a matrix release-controlling core in conjunction with an enteric coat. Lamotrigine release from the EC-MR tablet in the gastric phase is regulated by an aperture made in the enteric coat. The enteric coat is designed to dissolve when the pH of the surrounding medium exceeds 5.5. Under fasted conditions, this threshold pH value is typically encountered when the tablet enters the small intestine. The intake of food would appear to cause enteric coat disintegration within the stomach, thus enabling slightly more rapid drug release pre-intestinal transit.

The observed between-subject CV for AUC(0-∞) of lamotrigine was 32.3% and for Cmax of lamotrigine it was 19.6%.

Figure: Mean Serum Lamotrigine Concentration Time Profiles



A summary of the primary comparisons of interest for AUC(0-∞) and Cmax is presented in the following Table:

Table: Comparison between regimens for primary pharmacokinetic parameters

Comparison (Test : Reference)	Parameter	Geometric LS mean-test	Geometric LS mean-reference	Ratio	90% CI
200mg lamotrigine EC-MR, fed : 200mg lamotrigine EC-MR, fasted	AUC(0-∞) (ng.h/mL)	122147.4	118874.8	1.03	(0.92, 1.14)
	Cmax (ng/mL)	2201.9	1984.1	1.11	(1.04, 1.19)

For both AUC(0-∞) and Cmax, the 90% confidence interval of the ratio 200 mg lamotrigine EC-MR, fed: 200mg lamotrigine EC-MR, fasted lay completely inside the equivalence range 0.80 to 1.25 indicating a lack of effect of food on AUC(0-∞) and Cmax of lamotrigine.

On average, there was a marginal increase of 3% in AUC(0-∞) of lamotrigine when administered after food compared to fasted. The 90% confidence interval indicates that the true difference lies between a decrease of 8% and an increase of 14%.

There was a slight increase of 11% on average in Cmax of lamotrigine when administered after food compared to fasted. The 90% confidence interval indicates that the true difference lies between an increase of 4% and 19%.

An additional secondary analysis on AUC(0-∞) and Cmax of lamotrigine was performed as a sensitivity analysis to account for covariates gender and body weight in the analysis using the same model as above but including gender and body weight as covariates. The conclusions from these analyses are the same as those from the primary analysis.

Safety:

Fewer subjects receiving 200 mg lamotrigine EC-MR in fasted conditions experienced drug related AEs than those receiving the drug in fed treatment group. In fasted conditions there were 7 drug related AEs in n = 6 out of 47 subjects (13%) versus 13 drug related AEs in n = 11 out of 48 subjects (23%) in fed conditions. All AEs reported were either mild or moderate in a nature. AEs were headache, dizziness, somnolence, nausea, pain in extremity and night sweats

Conclusions:

Lack of effect of food was demonstrated on the pharmacokinetics of 200 mg lamotrigine enteric coated modified release tablets. The 90% confidence intervals for AUC(0-∞) and Cmax of 200 mg lamotrigine EC-MR after food, relative to the fasted state, lay completely inside the pre-specified equivalence range of 0.80 to 1.25.

LAM100017: An open-label study in healthy volunteers to evaluate the repeat dose pharmacokinetics, dose strength equivalence, dose proportionality, safety and tolerability of lamotrigine enteric coated modified release tablets and its relative bioavailability to lamotrigine immediate release tablets.

Objectives:

Primary:

- To characterize the pharmacokinetic profile of lamotrigine when administered as repeated oral doses of the EC-MR, and IR tablet formulation at daily doses of 25, 50, 100 and 200 mg.
- To explore the dose proportionality of lamotrigine when administered as repeated oral doses of the EC-MR tablet formulation at doses of 25, 50, 100 and 200 mg.
- To demonstrate dose strength equivalence of lamotrigine when administered as the EC-MR tablet formulation at doses of 50, 100 and 200 mg.
- To assess the relative bioavailability of lamotrigine EC-MR (QD) compared to lamotrigine IR (BID) at doses of 50, 100 and 200 mg/day.

Secondary:

- To assess the safety and tolerability of repeated oral doses of lamotrigine when administered as an EC-MR tablet formulation at doses of 25, 50, 100 and 200 mg, and when administered as the IR tablet formulation.

The study design is as follows:

Study center: (b) (4)
Methodology: The study was conducted using a parallel group, open-label design in a total of 44 healthy, male and female subjects (22 subjects per arm to provide evaluable data in at least 14 subjects/arm). After screening, subjects were randomized in equal numbers to one of two parallel groups: Lamotrigine IR (group A): IR lamotrigine titrated from a starting dose of 25 mg once a day to a final dose of 100 mg twice daily, using a standard lamotrigine titration schedule. Lamotrigine EC-MR (group B): EC-MR lamotrigine titrated from a starting dose of 25 mg once a day to a final dose of 200 mg once a day, using an equivalent titration schedule.

Titration Schedule for LAM10017

Day	Regimen Lamotrigine IR (Group A)	Lamotrigine EC-MR (Group B)
1 - 14	25 mg QD	25 mg QD
15 - 28	25 mg BID	50 mg QD (1x50 mg tablet)
29 - 33	25 mg BID	50 mg QD (2x25 mg tablets)
34 - 47	50 mg BID (2x25 mg tablet)	100 mg QD (1x100 mg tablet)
48 - 52	50 mg BID (2x25 mg tablet)	100 mg QD (2x50 mg tablets)
53 - 66	100 mg BID (1x100 mg tablet)	200 mg QD (1x200 mg tablet)
67 - 71	100 mg BID (1x100 mg tablet)	200 mg QD (2x100 mg tablets)
72 - 73	50 mg BID (2x25 mg tablet)	100 mg QD (1x100 mg tablet)
74 - 75	25 mg BID	50 mg QD (1x50 mg tablet)

Subjects attended the clinic for each dose change of the titration schedule and remained overnight in the clinic on the following up-titration days; Day 1, 15, 29, 34, 48, 53, and 67.

Pharmacokinetic Assessments:
Samples were taken predose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 36, 48, 72, 96, 120 and 144 hours following dosing (32 samples).

Serum samples were assayed for lamotrigine using a method based upon solid phase extraction followed by LC/MS/MS employing positive-ion Turbo Ion Spray ionization (lower limit of quantification (LLQ) 4.00 ng/mL).

Study LAM10017: Serum concentrations of lamotrigine in QC samples			
	Nominal Concentrations		
	QC 1	QC 2	QC 3
	15.00 ng/mL	350.00 ng/mL	3500.00 ng/mL
Overall Mean	15.1	348.4	3676.2
S.D.(within run means)	0.7	10.9	121.7
Precision(%CV)	4.5	3.1	3.3
Average Bias %	0.9	-0.5	5.0
n	88	90	90
Average Within Run Precision (%)	4.1	3.7	3.1
Between Run Precision (%)	0.2	Negligible	0.2

Number of subjects:

Number of Subjects	Lamotrigine IR (Group A)	Lamotrigine EC-MR (Group B)	Total
Planned, N	22	22	44
Randomized, N	33	27	60
Completed, n (%)	17 (52%)	19 (70%)	36 (60%)
Total Withdrawn (any reason), n (%)	16 (48%)	8 (30%)	24 (40%)
Withdrawn due to Serious Adverse Event, n (%)	0	0	0
Withdrawn due to Adverse Events, n (%)	2 (6%)	3 (11%)	5 (8%)
Withdrawn due to Protocol Violation, n (%)	2 (6%)	0	2 (3%)
Subject decided to withdraw from study, n (%)	12 (36%)	5 (19%)	17 (28%)

Treatment administration:
Subjects were dosed at the Unit for each dose increment in the titration schedule, all other dosing was at home and administered by the subject. Dosing occurred at approximately 08:00h and 22:00h for morning and evening doses respectively. The batch numbers used are given below:

Treatment	Drug	Dose/Form/Route	Frequency/Duration	Batch Number	Expiry Date
A	lamotrigine IR	25 mg/tablet/oral	QD/Day 1-14	5ZP8034	(b) (4)
		25 mg/tablet/oral	BID/Day 15-33	5ZP8034	
		50 mg/2 x 25 mg tablets/oral	BID/Day 34-52	5ZP8034	
		100 mg/1 x 100 mg tablet/oral	BID/Day 53-71	5ZP8452	
		50 mg/2 x 25 mg tablets/oral	BID/Day 72-73	5ZP8034	
		25 mg/tablet/oral	BID/Day 74-75	5ZP8034	
B	lamotrigine EC-MR	25 mg/tablet/oral	QD/Day 1-14	4ZM0904	
		50 mg/1 x 50 mg tablet/oral	QD/Day 15-28	4ZM3506	
		50 mg/ 2 x 25 mg tablets/oral	QD/Day 29-33	4ZM0904	
		100 mg/1 x 100 mg tablet/oral	QD/Day 34-47	4ZM0907	
		100 mg/2 x 50 mg tablets/oral	QD/Day 48-52	4ZM3506	
		200 mg/1 x 200 mg tablet/oral	QD/Day 53-66	4ZM6918	
		200 mg/2 x 100 mg tablets/oral	QD/Day 67-71	4ZM0907	
		100 mg/1 x 100 mg tablet/oral	QD/Day 72-73	4ZM0907	
		50 mg/ 1 x 50 mg tablet/ oral	QD/Day 74-75	4ZM3506	

Criteria for evaluation:
Primary:
• Steady state AUC(0-τ) or CL/F, Cmax and Cτ of lamotrigine.
Secondary:
• Tmax and fluctuation index of lamotrigine.
• Adverse events, changes in biochemistry, hematology, urinalysis parameters, electrocardiogram parameters, blood pressure and heart rate.

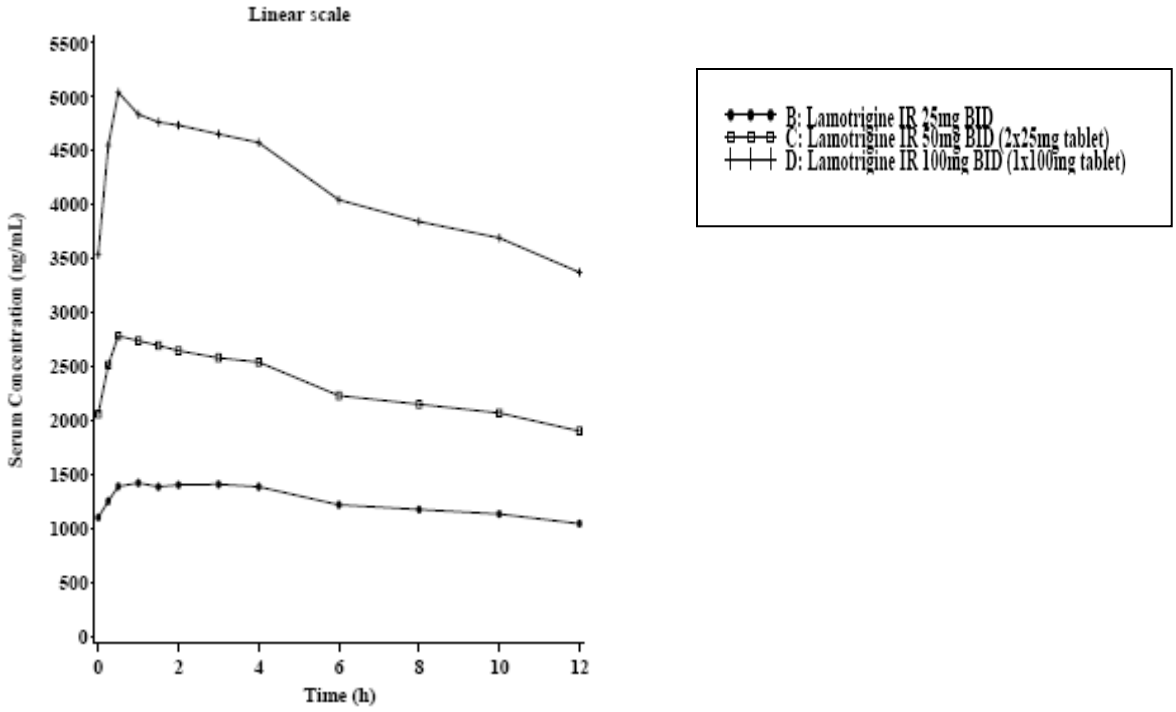
Pharmacokinetic Results:

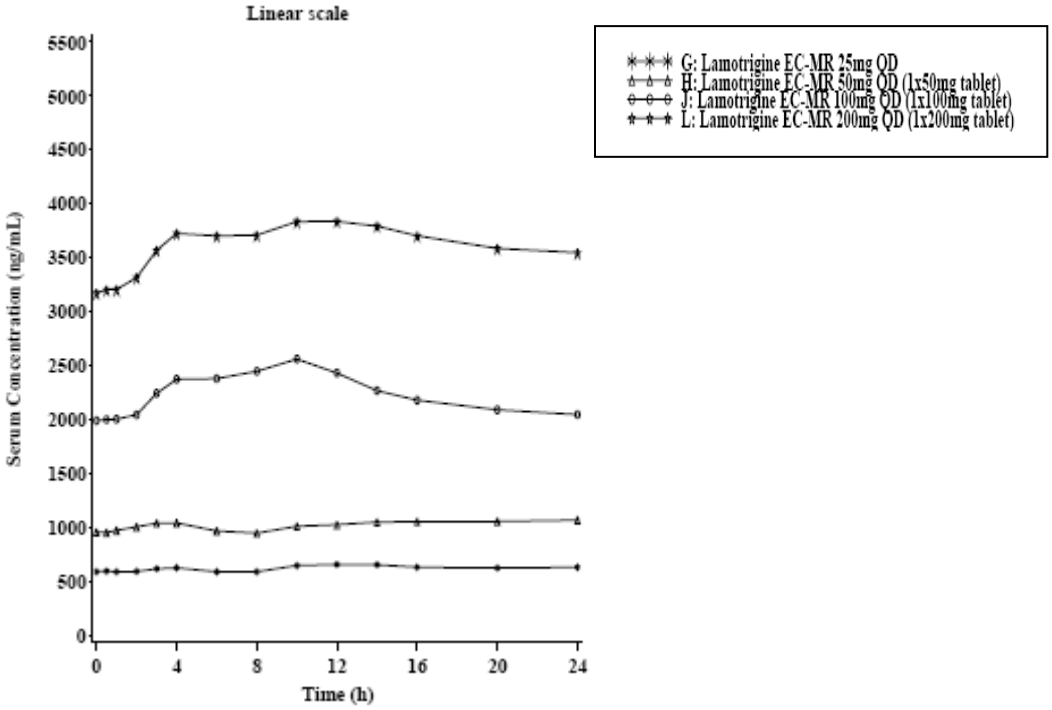
A summary of the geometric mean (CVb%) pharmacokinetic parameters is presented below.

Treatment	Formulation	N[1]	N[2]	AUC(0-τ) (ug.h/mL) (CVb%)	Cmax (ug/mL) (CVb%)	Tmax[3] (h)	Fluctuation Index[3]
25mg BID	IR	23	23	14.4 (27.7)	1.46 (26.4)	1.00 (0.25, 4.00)	0.35 (0.22-0.63)
50mg BID (2x25mg)	IR	22	17	26.8 (26.4)	2.87 (21.0)	0.50 (0.25, 1.50)	0.40(0.23-0.77)
100mg BID (1x100mg)	IR	17	17	47.9 (27.9)	5.13 (23.1)	0.50 (0.25, 3.07)	0.42(0.28-0.72)
25mg QD	EC-MR	21	21	14.5 (24.6)	0.669 (24.3)	14.0 (3.00, 23.92)	0.13 (0.05-0.2)
50 mg QD (1x50mg)	EC-MR	21	20	23.5 (31.5)	1.08 (31.0)	14.0 (0.00, 23.92)	0.095 (0.02-0.2)
50mg QD (2x25mg)	EC-MR	20	19	25.9 (24.1)	1.19 (24.1)	12.0 (0.00, 23.92)	
100mg QD (1x100mg)	EC-MR	19	19	52.1 (26.9)	2.56 (25.7)	10.0 (3.00, 14.00)	0.29 (0.07 -0.66)
100mg QD (2x50mg)	EC-MR	19	19	49.8 (37.4)	2.42 (37.1)	12.0 (2.02, 23.93)	
200mg QD (1x200mg)	EC-MR	19	18	87.4 (26.2)	4.22 (26.9)	10.0 (0.50, 23.92)	0.22 (0.12-0.44)
200mg QD (2x100mg)	EC-MR	19	18	89.4 (33.2)	4.50 (31.7)	10.0 (6.00, 23.92)	

1. number of individuals providing a parameter
2. number included in the summary statistic
3. median (range)

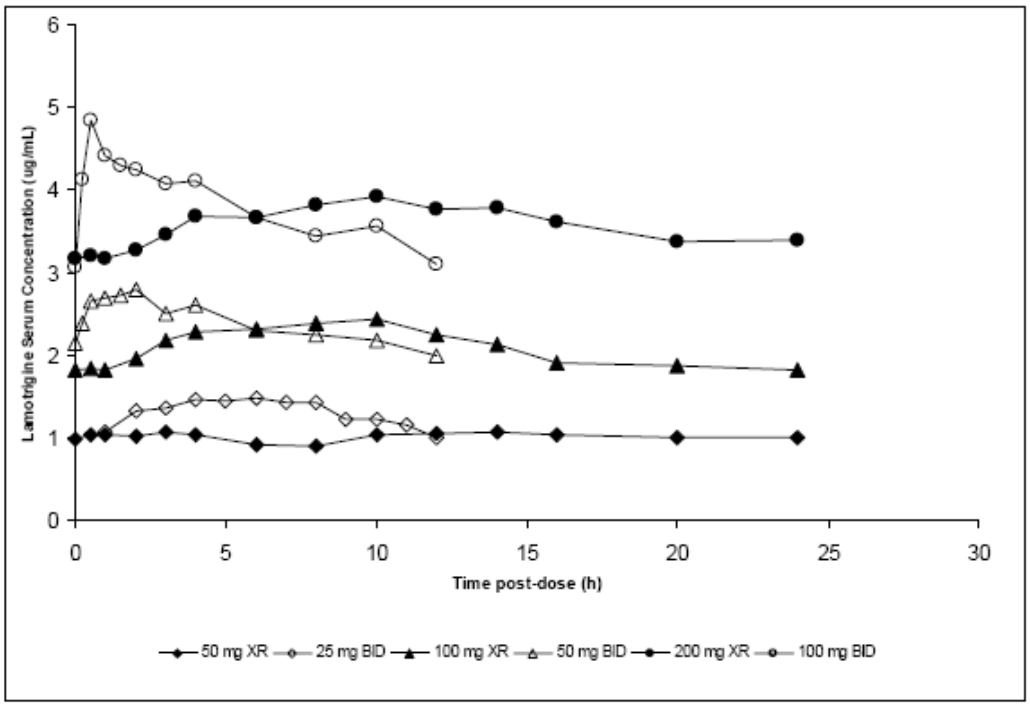
The plasma concentration time profiles for the IR and ER dosage strengths is given below:





The median serum lamotrigine concentrations showing the IR and ER comparisons is shown in the following Figure:

Figure: Median Lamotrigine Serum Concentrations Following Administration of Lamotrigine Extended Release (XR) Tablets (50, 100 and 200 mg) and Lamictal (25, 50 and 100 mg BID)



Dose Strength Equivalence:

In order to demonstrate dose strength equivalence within the lamotrigine EC-MR arm the following comparisons were made with point estimates and 90% confidence intervals:

- 2x25mg EC-MR tablet (Day 33) vs. 1x50mg EC-MR tablet (Day 28)
- 2x50mg EC-MR tablet (Day 52) vs. 1x100 mg EC-MR tablet (Day 47)
- 2x100mg EC-MR tablet (Day 71) vs. 1x200mg EC-MR tablet (Day 66)

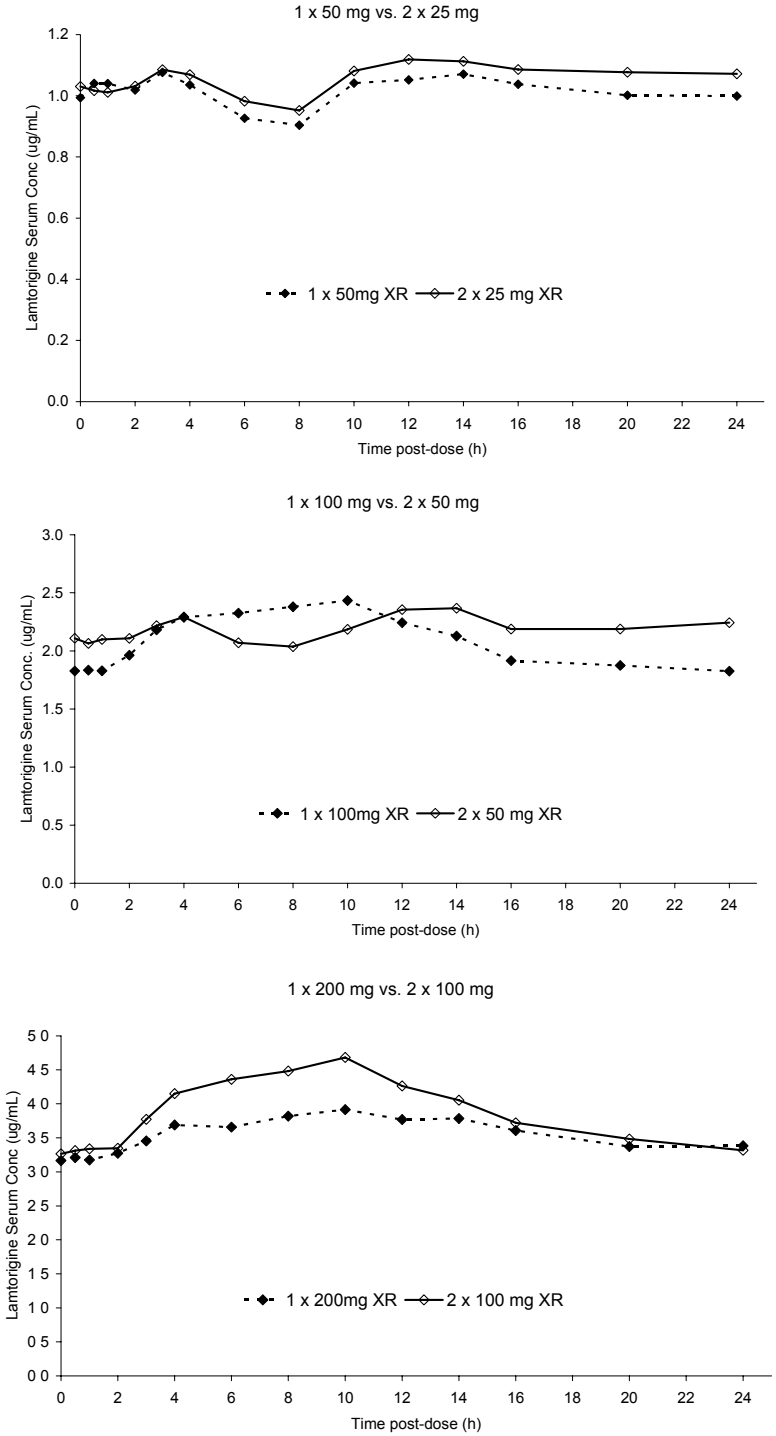
A summary of the statistical assessment of dose strength equivalence of the EC-MR once daily formulation is presented in the following Table.

Table: Summary Table of Analysis of the Steady-State Dose Strength equivalence of the Lamotrigine EC-MR formulation: 50, 100 and 200 mg comparisons.

Parameter	Lamotrigine EC-MR		Geometric LSMean		Ratio (Test:Ref)	90% CI for ratio
	Test	Ref.	Test	Ref.		
AUC(0-τ) (ug.h/mL)	2x25mg	1x50mg	26.1268	23.4861	1.112	(1.009,1.227)
	2x50mg	1x100mg	50.2830	52.5542	0.957	(0.867,1.056)
	2x100mg	1x200mg	91.9496	89.8688	1.023	(0.925,1.132)
Cmax (ug/mL)	2x25mg	1x50mg	1.1984	1.0779	1.112	(1.002,1.234)
	2x50mg	1x100mg	2.4336	2.5816	0.943	(0.849,1.047)
	2x100mg	1x200mg	4.6111	4.3269	1.066	(0.957,1.187)
Cτ (ug/mL)	2x25mg	1x50mg	1.0510	0.9367	1.122	(1.005,1.252)
	2x50mg	1x100mg	1.9945	1.8935	1.053	(0.943,1.177)
	2x100mg	1x200mg	3.2302	3.3652	0.960	(0.857,1.076)

For AUC(0-τ) and Cmax, the ratio's and 90% confidence intervals for the respective comparison of the two tablets versus the one tablet, fell within the pre-defined equivalence range of 0.8-1.25. Evaluation of trough concentrations, Cτ, also had 90% confidence intervals lying within the equivalence range of 0.8-1.25, with the exception of the 50 mg dose comparison (2 x 25 mg vs. 1 x 50 mg QD), where the upper 90% CI was marginally above the acceptance range (1.252).
Median serum concentration-time profiles for lamotrigine comparing the 1x50 mg versus 2x25 mg, 1x100 mg versus 2x50 mg and 1x200 mg versus 2x100 mg dose strengths are presented in the following Figure:

Figure **Median Serum Lamotrigine Concentration-Time Profiles Following Administration of (1x50 mg vs. 2x25 mg), (1x100 mg vs. 2x50 mg) and (1x200 mg vs. 2x100 mg) lamotrigine XR tablets**



Dose Proportionality EC-MR

In order to assess dose proportionality of lamotrigine EC-MR (25 mg on Day 14, 50 mg on Day 28, 100 mg on Day 47, 200 mg on Day 66), point estimates and 90% confidence intervals were computed for the slope of AUC(0-τ) and Cmax versus dose for that arm. Summary of the statistical assessment of dose proportionality of the EC-MR dose range of 25 -200 mg, as assessed by the power model:

Table: Summary Table of Statistical Analysis of Dose Proportionality of Lamotrigine EC-MR (Power Model) for AUC(0-tau), Cmax and Ctau. Dose Range 25-200 mg.

Parameter	Adjusted Mean Slope	Standard Error	90% CI for adjusted mean slope
AUC(0-τ) (ug.h/mL)	0.897	0.026	(0.853,0.941)
Cmax (ug/mL)	0.928	0.028	(0.881,0.975)
[a]Cτ (ug/mL)	0.850	0.028	(0.803, 0.897)

The results showed a less than proportional increase with increasing dose in terms of AUC(0-τ) and Cmax, with lower 90% CI for the adjusted mean slope lying outside the pre-defined limits of 0.893 – 1.107. Based on these results and visual evaluation of the data, a secondary analysis was performed evaluating the dose range of 50-200 mg, using the power model. The pre-defined limits for the 90% CI for the adjusted mean slope was 0.8391-1.1609 for this dose range. Dose proportionality was confirmed for both AUC(0-τ) and Cmax across the dose range of 50-200 mg.

Summary of the statistical assessment of dose proportionality of the EC-MR dose range of 50-200 mg, as assessed by the power model:

Table: Summary Table of Statistical Analysis of Dose Proportionality of Lamotrigine EC-MR (Power Model) for AUC(0-tau) and Cmax. Dose Range 50 - 200 mg.

Parameter	Adjusted Mean Slope	Standard Error	90% CI for adjusted mean slope
AUC(0-τ) (ug.h/mL)	0.969	0.045	(0.892, 1.046)
Cmax (ug/mL)	1.004	0.054	(0.920, 1.008)
[a]Cτ (ug/mL)	0.924	0.048	(0.842, 1.005)

Overall figure showing dose proportionality is shown in the following Figure:

Figure 11.18
Individual AUC(0-24) values at each dose for regimens G, H, J & L
together with the geometric mean AUC(0-24) values for each dose

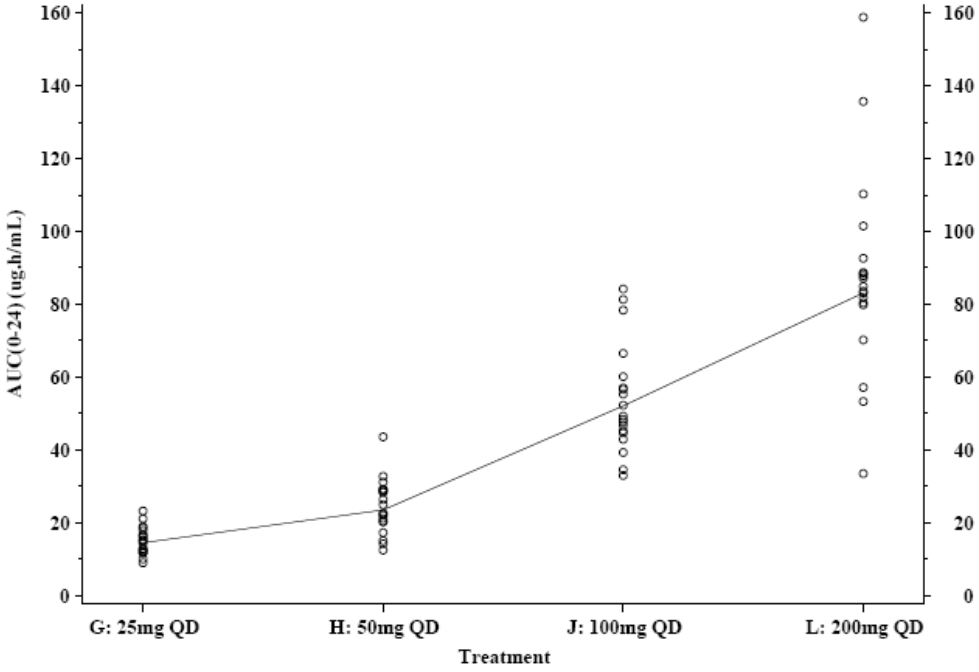
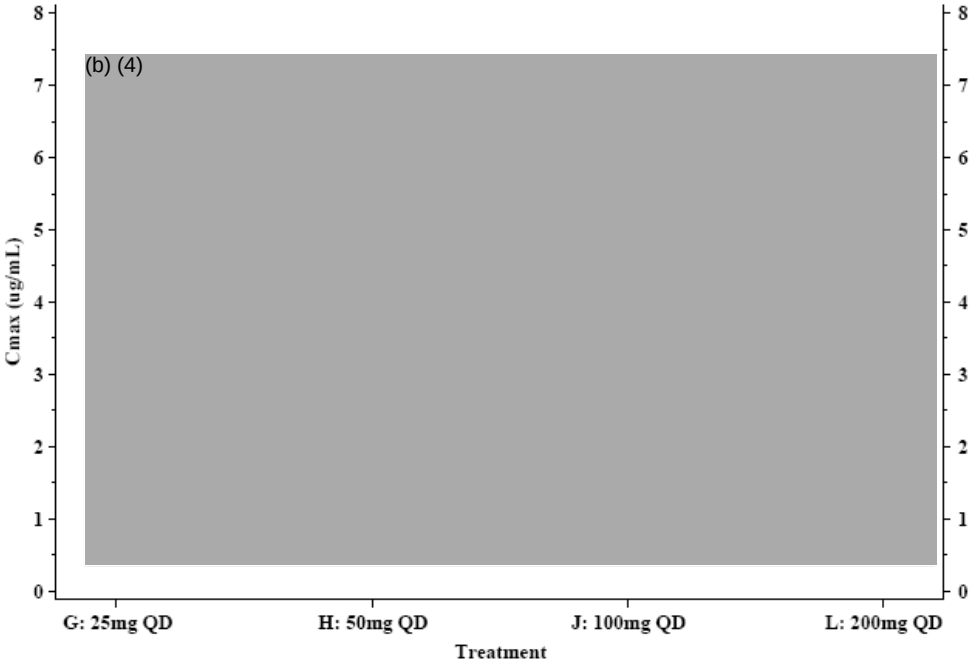


Figure 11.19
Individual Cmax values at each dose for regimens G, H, J & L
together with the geometric mean Cmax values for each dose



Cτ follows a similar pattern too.

Dose proportionality IR

Dose proportionality was also evaluated for the IR formulation across the dose range of 25-100 mg b.i.d ,using the power model. A summary of the statistical assessment of dose proportionality (power model) of lamotrigine IR is presented below.

Parameter	Adjusted Mean Slope	Standard Error	90% CI for adjusted mean slope
AUC(0-τ) (ug.h/mL)	0.893	0.024	(0.852, 0.934)
Cmax (ug/mL)	0.926	0.027	(0.881, 0.971)

The analysis confirmed dose proportionality of the IR formulation at steady-state across the dose range of 25 – 100 mg bid, in terms of AUC(0-τ) and Cmax with 90% confidence intervals for the adjusted mean slope lying within the pre-defined limits of 0.8391 to 1.1609.

Comparison of the Disposition of the IR and EC-MR Formulations at Steady-State

A slightly reduced average concentration over the dosing interval was observed with the EC-MR formulation in comparison to the IR formulation, as described by the parameters Cavg and Cτ. These are summarized in the following Table.

Table: Summary Table of average concentration and fluctuation index for the IR and EC-MR dosing regimens

	N	n	Cavg (ug/mL)	Flucutation Index[a]	Cτ (ug/mL)	Tmax (h)[b]
25 mg BID	23	23	1.20 (27.6)	0.35 (0.22 – 0.63)	1.03 (30.7)	1.00 (0.25 – 4.00)
50 mg BID (2 x 25 mg)	22	17	2.23 (26.5)	0.40 (0.23 – 0.77)	1.90 (30.6)	0.50(0.25- 1.50)
100 mg BID (1x100 mg)	17	17	3.99 (27.9)	0.42 (0.28 – 0.72)	3.3 (30.9)	0.50 (0.25 – 3.07)
25 mg QD	21	21	0.61 (24.6)	0.13 (0.05 – 0.2)	0.59(24.6)	14.0 (3.00 – 23.92)
50 mg QD (1x50 mg)	21	20	0.98 (31.6)	0.095 (0.02 – 0.20)	0.94 (39.4)	14.0 (0.00 – 23.92)
100 mg QD (1x100 mg)	19	19	2.17 (27.0)	0.29 (0.07 – 0.66)	1.93 (31.0)	12.0 (3.00 – 14.00)
200 mg QD (1x200 mg)	19	18	3.64 (26.2)	0.22 (0.12 – 0.44)	3.36 (27.3)	10.0 (0.50 – 23.92)

The overall fluctuation index for the IR formulation was consistent across all dose levels with a mean range of 0.35 -0.42, in contrast the fluctuation for the EC-MR formulation was much lower, but was higher for the 100 and 200 mg QD regimens with mean indices of 0.29 and 0.22, in comparison to the lower doses with mean fluctuation indices of 0.13 and 0.095. In terms of time to maximum concentrations, for the EC-MR formulation, this

was achieved between 10 and 14 hours post-dose at steady-state, in comparison to the IR with a median Tmax of 0.5 -1 h post-dose.

Relative Bioavailability
A summary of the assessments of the relative bioavailability of the EC-MR formulation at steady-state in comparison to the IR formulation is presented below:

Table: Summary of Statistical Analysis of Relative Bioavailability of Lamotrigine EC-MR versus respective IR daily dose.

Parameter	Dose	Test	Ref.	Geom. LSMean Test	Geom. LsMean Ref.	Ratio	90% CI for Ratio
Dose Normalized AUC(0-τ) (h/L)	50mg	50 mg QD EC-MR	25mg BID IR	0.4694	0.5772	0.813	(0.708, 0.935)
	100mg	100mg QD EC-MR	50mg BID IR	0.5207	0.5366	0.970	(0.834, 1.129)
	200mg	200mg QD EC-MR	100mg BID IR	0.4369	0.4787	0.913	(0.783, 1.064)
CL/F (L/hr)	50mg	50mg QD EC-MR	25mg BID IR	2.1303	1.7325	1.230	(1.070,1.413)
	100mg	100mg QD EC-MR	50mg BID IR	1.9207	1.8637	1.031	(0.885,1.199)
	200mg	200mg QD EC-MR	100mg BID IR	2.2890	2.0891	1.096	(0.940,1.278)
Cmax (ug/mL)	50mg	50mg QD EC-MR	25mg BID IR	1.0779	1.4634	0.737	(0.647,0.839)
	100mg	100mg QD EC-MR	50mg BID IR	2.5614	2.8678	0.893	(0.775,1.029)
	200mg	200mg QD EC-MR	100mg BID IR	4.2223	5.1253	0.824	(0.714,0.951)
Cτ (ug/mL)	50mg	50mg QD EC-MR	25mg BID IR	0.9367	1.0307	0.909	(0.777,1.063)
	100mg	100mg QD EC-MR	50mg BID IR	1.9305	1.9031	1.014	(0.853,1.206)
	200mg	200mg QD EC-MR	100mg BID IR	3.3557	3.3097	1.014	(0.851,1.208)

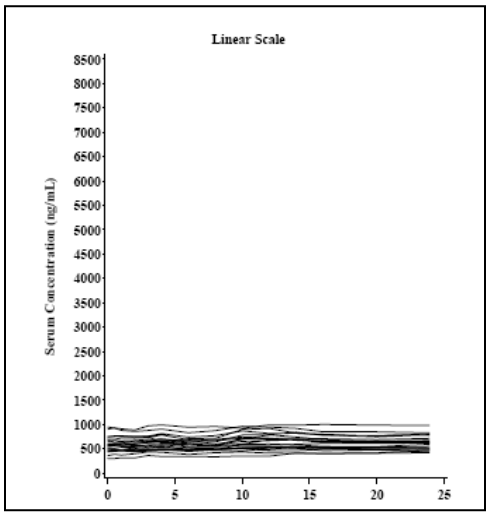
- In terms of dose-normalized AUC(0-τ), the 50 mg, 100 mg and 200 mg EC-MR formulations show a mean relative bioavailability of 81 %, 97% and 91%, respectively, compared to the IR formulations at the same daily dose.
- Steady-state trough concentrations for all three doses were close to 100 % in comparison to the IR formulation.

- In terms of Cmax, the maximum concentration of the EC-MR formulation was lower than the IR by approximately 10-30 % across the dose range.

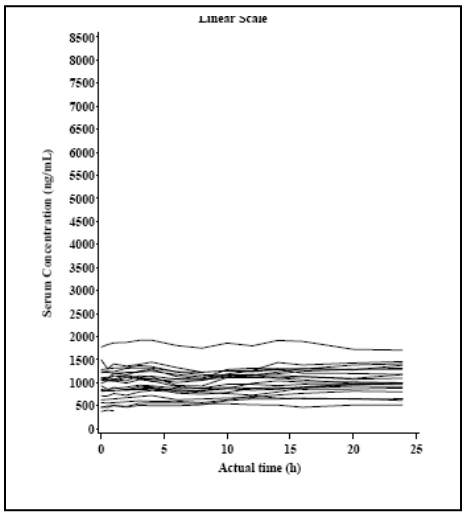
Figures showing these comparisons are given earlier.

Variability:

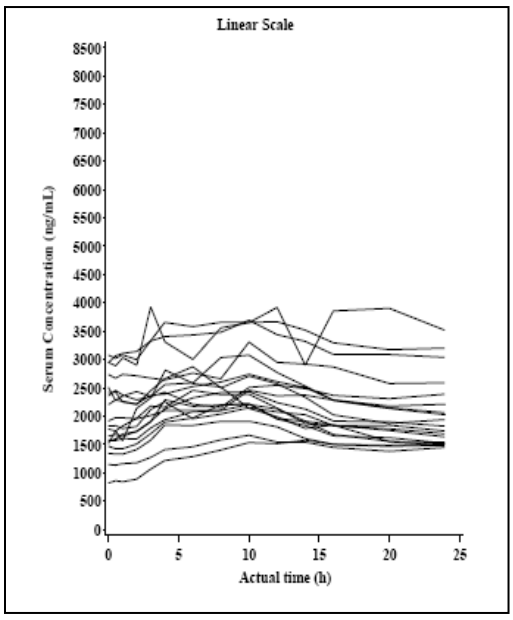
In general for all four strengths, the % CV is similar (20-35%). See spaghetti plots of all four strengths:



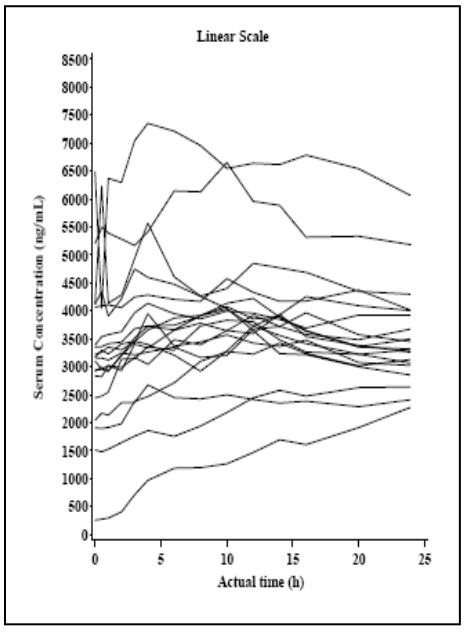
25mg ER



50 mg ER



100 mg ER



200 mg ER

Safety:

- There were no serious adverse events during the study. The number of subjects who reported at least one AE was higher in the Lamotrigine EC-MR dosing group (74%) than in the Lamotrigine IR dosing (45%). The frequency of AEs was not clearly dose-dependent. Of the total AEs reported seven were moderate in intensity and all the remaining AEs were mild.
- There were five subject withdrawals due to AEs during the study; two from Lamotrigine IR group and three from Lamotrigine EC-MR group. These were attributed to three mild and two moderate rashes. Four of the five rashes were considered to be related to the investigational product and four required treatment with concomitant medication. The most commonly reported AE was headache.
- There were no clinically significant laboratory tests, vital sign recordings or ECG findings during the study.

Conclusions:

- Dose strength equivalence was demonstrated for all comparison of the EC-MR tablet formulation at doses of 50,100 and 200 mg in terms of AUC(0-τ) and Cmax. For Cτ dose strength equivalence was achieved for 2x50mg vs 1x100mg, 2x100mg vs 1x200mg QD regimens but the upper limit of the 90% confidence interval for 2x25mg vs 1x50mg QD was marginally above the acceptance range (1.252).
- Dose proportionality of lamotrigine was observed following repeat oral administration over the dose range of 50-200 mg QD dosing of the EC-MR formulation, however a slightly less than proportional increase with increasing dose was observed over the dose range of 25-200 mg dose range of the EC-MR formulation. Dose proportionality for the IR formulation was observed for the IR formulation across the dose range of 25-100 mg bid.
- The relative bioavailability of the EC-MR formulation in comparison to the IR formulation demonstrated a slightly lower daily exposure in comparison to the IR formulation with dose normalized AUC ratio's of on average 81%, 97% and 91% for the 50, 100 and 200 mg QD doses, in comparison their respective IR doses. Lower mean maximum concentrations of the EC-MR formulation were observed, approximately 10-30 % lower, whilst achieving comparable mean trough concentrations over the dosing interval.

LAM102611: A randomized, single blind, parallel group, placebo control study to investigate the effect of repeat oral doses of esomeprazole on a single oral dose of 200 mg lamotrigine EC-MR in healthy volunteers

Study Rationale:

The lamotrigine ER formulation has an enteric coat that is sensitive to changes in gastric pH. Due to the potential for concomitant use of lamotrigine with agents that increase gastric pH in the target population, this study was conducted in order to evaluate the effect of repeated oral doses of esomeprazole - a proton pump inhibitor - on the pharmacokinetics of a single dose of 200 mg lamotrigine EC-MR.

A dose of 200 mg lamotrigine was selected as it represented the highest tablet strength of the EC-MR formulation.

A dose of 40 mg of esomeprazole was administered since this is the highest approved dosage on the market.

A parallel-group design was selected to avoid repeated administration of single doses of lamotrigine to healthy subjects; it was considered that repeated administration of single doses of lamotrigine higher than of 25 mg, rather than using the recommended dose titration schedule, might have increased risk of skin rash.

Objectives:

Primary:

- To estimate the effect of repeated oral doses of 40 mg esomeprazole on the pharmacokinetics of a single oral dose of 200 mg lamotrigine EC-MR in healthy volunteers

Secondary:

- To assess the safety and tolerability of repeated oral doses of 40 mg esomeprazole and a single oral dose of 200 mg lamotrigine EC-MR in healthy volunteers

The study design is as follows:

Study center: (b) (4)
Methodology: The study was conducted using a parallel-group, randomized, single-blind design with a total of 61 healthy male and female subjects in order to allow 30 evaluable subjects per arm. After screening, the subjects were randomized to one of 2 parallel groups to receive either esomeprazole or placebo once daily for 12 days. On Day 7, all subjects in both groups received one dose of 200 mg lamotrigine EC-MR.

Pharmacokinetic Assessments:
Blood samples were collected for quantitative pharmacokinetic analysis of lamotrigine at nominal times: pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 36, 48, 72, 96, 120 and 144 hours post-dose.

Serum samples were assayed for lamotrigine using a method based upon solid phase extraction followed by LC/MS/MS employing positive-ion Turbo Ion Spray ionization (lower limit of quantification (LLQ) 4.00 ng/mL).

Study LAM102611: Serum concentrations of lamotrigine in QC samples			
	Nominal Concentrations		
	QC 1	QC 2	QC 3
	15.00 ng/mL	350.00 ng/mL	3500.00 ng/mL
Overall Mean	15.1	354.4	3537.5
S.D.(within run means)	0.4	6.5	88.7
Precision(%CV)	2.5	1.8	2.5
Average Bias %	0.7	1.3	1.1
n	42	42	42
Average Within Run Precision (%)	2.2	0.8	1.1
Between Run Precision (%)	0.3	0.4	0.5

Number of subjects:

Number of Subjects	Placebo + Lamotrigine	Esomeprazole + Lamotrigine
Planned, N	30	30
Randomized, N	30	31
Completed, n (%)	30 (100%)	31 (100%)
Total Withdrawn (any reason), n (%)	0	0

There were all Caucasians in this Study

		Placebo + Lamotrigine (N=30)	Esomeprazole + Lamotrigine (N=31)
Sex, n (%)	Males Females	17 (57%) 13(42%)	19 (61%) 12 (39%)
Age, years	Mean SD	37.6 9.9	39.1 8.2

Treatment administration:

Treatment A = Placebo on Days 1 to 6
Treatment B = Placebo on Days 7 to 12 with 200 mg lamotrigine on Day 7
Treatment C = Esomeprazole 40 mg on Days 1 to 6
Treatment D = Esomeprazole 40 mg on Days 7 to 12 with 200 mg lamotrigine on Day 7
Subjects were randomized to one of the following two treatment groups:
Group A/B = Placebo / Placebo + 200 mg Lamotrigine
Group C/D = Esomeprazole 40 mg + 200 mg Lamotrigine

Drug	Dose/Form/Route	Frequency/Duration	Batch Number
Esomeprazole	40 mg/tablet/oral	Once daily for 12 days	GJ10258A1
Lamotrigine EC-MR	200 mg/tablet/oral	1 single dose on Day 7	051085317
Placebo not matching esomeprazole	not applicable/ tablet/oral	Once daily for 12 days	051108355

On Day 7 subjects were administered their dose of esomeprazole or placebo after an overnight fast from midnight the evening prior to dosing. Subjects took the dose with 240 mL of water. One hour later, they received a standard breakfast at the CPRU and a further 1 h later, they were dosed with 200 mg lamotrigine. Again, 240 mL of water was also permitted for dosing with 200 mg lamotrigine.

Pharmacodynamic Assessments:
In order to correlate the PK characteristics of lamotrigine to the increased gastric pH after repeated treatment with esomeprazole, pH-monitoring was performed on Day 7, starting pre-esomeprazole or placebo dose until 8 hours post-lamotrigine dose.
Prior to the study, electrodes were to be calibrated at pH 7 and pH 1. Subjects remained NPO (nothing by mouth) for at least 2 hours prior to insertion of the probe and the probe was to be correctly in place for at least 2 hours prior to dosing with lamotrigine.

Criteria for evaluation:
Primary:
• Single dose AUC(0-τ) or CL/F, Cmax and Cτ of lamotrigine.
Secondary:
• t_{max} and $t_{1/2}$ of lamotrigine
• Adverse events, changes in biochemistry, hematology, urinalysis parameters, electrocardiogram parameters, blood pressure and heart rate.
Assessment of intra-gastric pH via continuous monitoring for 8 hours after dosing of lamotrigine alone or in combination with esomeprazole

Pharmacokinetic Results:

A summary of lamotrigine pharmacokinetic parameters are summarized in the following Table:

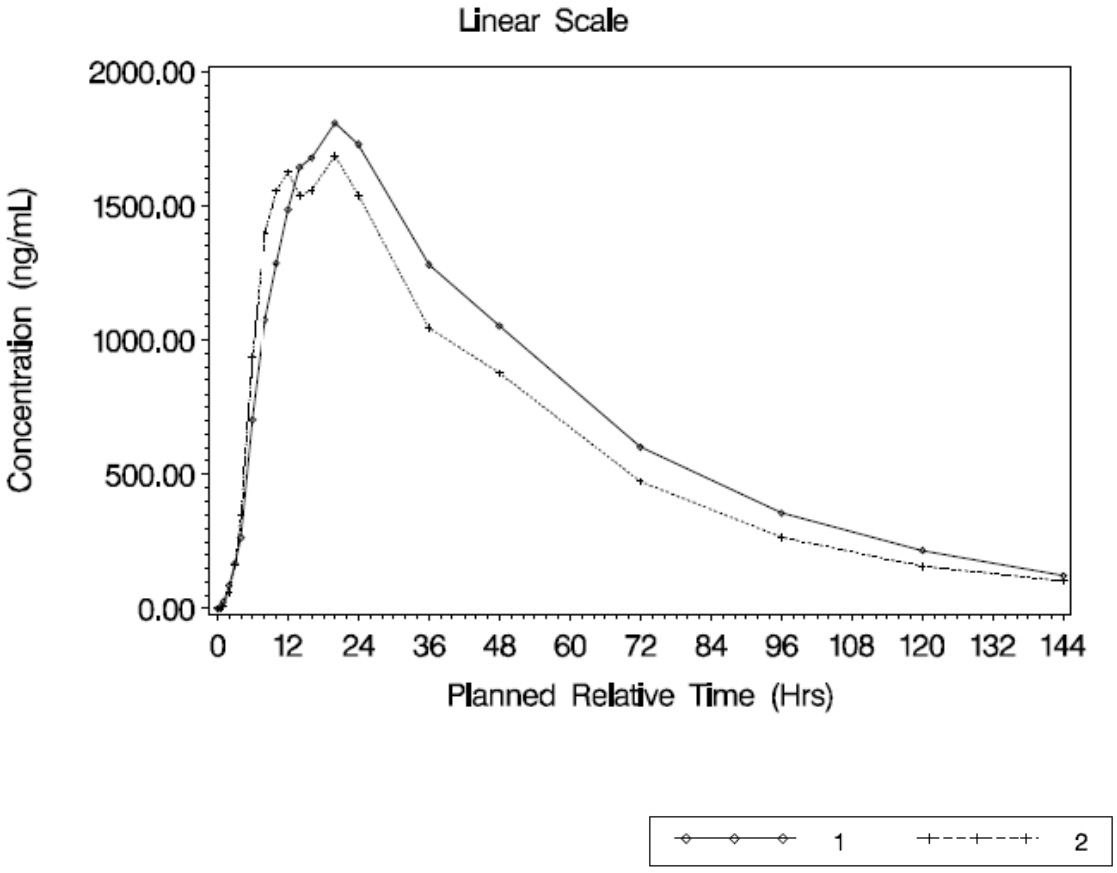
Table: Geometric Mean (CVb%) Lamotrigine Pharmacokinetic Parameters

Regimen	N	$AUC_{(0-\infty)}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[1]	$t_{1/2}$ (h)
A	31	90,732 (26.2)[2]	1847 (22.8)	12.0 (6.00-24.08)	29.5 (27.2)
B	30	102,634 (32.9)	1891 (23.0)	20.0 (10.00-24.12)	30.1 (22.1)

Data Source: Table 11.2 and Table 11.3
1. Median (range)
2. n=30
Regimen: A: Esomeprazole 40 mg + 200 mg Lamotrigine EC-MR
B: Placebo + 200 mg Lamotrigine EC-MR

- C_{max}, were achieved, with a shortened median t_{max}, by approximately 8 h, in the esomeprazole group in comparison to the lamotrigine + placebo group.
- An overall reduction in the total exposure, $AUC_{(0-\infty)}$ in the esomeprazole group in comparison to the lamotrigine with placebo group, reflecting the reduction in concentrations following attainment of peak concentrations.
- The terminal half-life, $t_{1/2}$ was similar between the two treatment groups.

Figure: Mean lamotrigine plasma concentrations of the two regimens



Note: LLQ = 4.0 ng/mL
1 = Placebo + 200mg Lamotrigine EC−MR, 2 = Esomeprazole 40mg + 200mg Lamotrigine EC−MR.
Subject 115 did not receive Esomeprazole dose in days 9 and 10 so concentration values beyond Day 7 + 48 hours for this subject have been excluded.

The results of the statistical analysis of the primary pharmacokinetic endpoints, $AUC_{(0-\infty)}$ and C_{max} and of lamotrigine when co-administered with esomeprazole compared to lamotrigine dosed with a placebo, are presented in the following Table

Table: Summary of Statistical Analysis of $AUC_{(0\text{-Infinity})}$ and C_{max} of Lamotrigine

Parameter	Comparison	Ratio[1]	90% CI
$AUC_{(0-\infty)}$	A : B	0.88	(0.78, 1.00)
C_{max}	A : B	0.98	(0.89, 1.08)

Data Source: Table 11.4

1. Ratio represents ratio of geometric LSmeans between regimens

Regimen:

A Esomeprazole 40 mg + 200 mg Lamotrigine EC-MR

B Placebo + 200 mg Lamotrigine EC-MR

- Following co-administration of lamotrigine with esomeprazole (40 mg), there was on average a 12% decrease in lamotrigine $AUC_{(0-\infty)}$ and a 2% decrease in C_{max}, compared to those observed in the lamotrigine with placebo group.
- The 90% confidence intervals show that the true decrease in $AUC_{(0-\infty)}$ lies between 0 and 22% , and for C_{max} lies between an increase of 8% and a decrease of 11%.
- The pooled between-subject CV's from the statistical analysis were 29.7% for $AUC_{(0-\infty)}$ and 22.9% for C_{max} of lamotrigine.

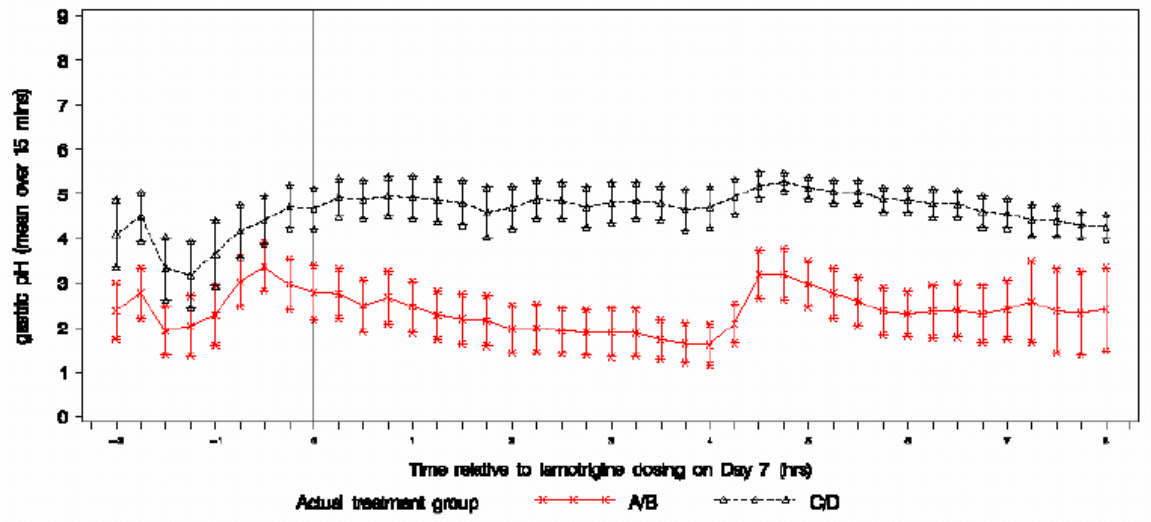
Pharmacodynamics

Gastric pH evaluation

Gastric pH-values were measured from –2 hours to +8 hours relative to lamotrigine dosing on Day 7. The value recorded for reporting was the mean value over every 15-minute interval (e.g. 15-minute time-point = mean over a 0-15 minutes time-period after the lamotrigine dose). Breakfast was served one hour before administration of lamotrigine and lunch 4 hours afterwards.

Twenty-nine (29) subjects in the esomeprazole + lamotrigine group and 25 subjects in the placebo + lamotrigine group were included in the summary statistics output. Some subjects were excluded due to technical problems with the probe.
A plot of mean and 95% CI for mean gastric pH over time by treatment group is shown in the following figure.

Figure: Plot of Mean and 95% CI for Gastric pH over Time by Treatment Group



Subjects 109, 133, 140 & 159 excluded due to problems with probe
A/B = Placebo + 200mg lamotrigine EC–MR
C/D = Esomeprazole 40mg + 200mg lamotrigine EC–MR

- The esomeprazole + lamotrigine treatment group showed higher levels of gastric pH over time than the placebo + lamotrigine group. This is consistent with the pharmacological action of a proton pump inhibitor such as esomeprazole.
- The addition of lamotrigine to esomeprazole did not appear to impact on the levels of gastric pH compared to prelamotrigine dosing.

Conclusions:

- Following co-administration of lamotrigine with 40 mg esomeprazole, there was on average a 12% decrease in $AUC_{(0-\infty)}$ (mean ratio of 0.88, 90% CI: 0.78 – 1.00) compared to that achieved in the lamotrigine with placebo group. However, maximum concentrations of lamotrigine, C_{max} were not affected, with on average a decrease of 2% (mean ratio of 0.98, 90% CI: 0.89 – 1.08). The median time to maximum concentration, t_{max}, was shortened by approximately 8.0 hours following co-administration with esomeprazole in comparison to lamotrigine with placebo, whilst the terminal half-lives were similar.
- Gastric pH levels in the esomeprazole+lamotrigine group were higher than those in the placebo+lamotrigine group.
- The addition of lamotrigine to esomeprazole does not appear to impact on the levels of gastric pH compared to pre-lamotrigine dosing.
- There were no serious adverse events during the study. There were no clinically significant laboratory tests, vital sign recordings or ECG findings during the study. Co-administration of esomeprazole does not appear to affect the tolerability of lamotrigine, as the adverse event profiles of lamotrigine + esomeprazole and lamotrigine + placebo were similar.

LEP 103944: An Open-label, Double Conversion Study to Characterize the Pharmacokinetics of Lamotrigine when Switching Patients with Epilepsy on LAMICTAL® Immediate-release to Extended-release Formulation and Vice Versa.

Objectives:

Primary:

- The primary objective of this study was to characterize the PK profile of LAMICTAL (LTG) when administered as an extended-release once daily (QD) formulation compared to a LTG-IR twice daily (BID) formulation in subjects with epilepsy already taking commercially available LAMICTAL.

Secondary:

- To assess the relative bioavailability of LTG extended-release (QD) compared to LTG-IR (BID) in subjects with epilepsy already taking commercially available LTG and
- To assess the safety and tolerability of LTG extended-release (QD) compared to LTG-IR (BID) in subjects with epilepsy.

The study design is as follows:

Study center: 12 centers in US
Methodology: Subjects on a stable regimen of twice daily commercial LAMICTAL and up to two additional concomitant AEDs were enrolled and grouped based on their concomitant AED medications, as follows, as these drugs have been shown to have an effect on the PK profile for LTG-IR: • **Group 1-Neutral**: Subjects taking LTG-IR monotherapy or LTG-IR and the following non-inducing, non-inhibiting AEDs (oxcarbazepine, levetiracetam, gabapentin, topiramate, zonisamide, tiagabine) • **Group 2-Induced**: Subjects taking LTG-IR and the following enzyme inducing anti-epileptic drugs (EIAEDs) (carbamazepine, phenytoin, phenobarbital, primidone) with or without another AED other than VPA • **Group 3-Inhibited**: Subjects taking LTG-IR and VPA with or without another noninducing AED. Subjects could not be on VPA and an EIAED for the purposes of this study. The study consisted of four phases:

Phase	Duration of Phase	Purpose
Screen	<1 week	Determine eligibility
Baseline (IR Treatment Phase)	2 weeks	Continue on twice daily LTG-IR
Extended-release Treatment Phase	2 weeks	Switch to once daily LTG extended-release
IR Phase	1 week	Switch back to twice daily LTG-IR
(At EOS visit)		Switch to commercially available LTG

The expected total duration of a subject's participation in this study was approximately five weeks. At the end of the study, subjects resumed taking commercially available LAMICTAL and did not taper off study drug.

Pharmacokinetic Assessments:

Visit 2 (Day 13):
One predose sample was collected to confirm steady state on the LTG-IR formulation prior to the 48 hour inpatient period on Days 14 and 15.

Visit 3 (Days 14 and 15):
Blood samples were collected over this 48-hour period as follows:
• Steady-State IR: Day 14 (21 blood samples) - One predose blood sample was collected and 20 blood samples were collected after the morning dose of LTG-IR at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 22 and 24 hours (the next morning prior to the first dose of LTG extended-release)
• Day of Conversion to Extended-release: Day 15/16 (13 blood samples) - Thirteen samples were collected after the first dose of LTG extended-release at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours (the next morning, before the LTG extended release dose for Day 16)

Visit 4 (Day 27):
One predose sample was collected to confirm steady state on the LTG extended-release formulation prior to the 48-hour inpatient period on Days 28 and 29.

Visit 5 (Days 28 and 29):
Blood samples were collected over this 48-hour period as follows:

• Steady-State Extended-release: Day 28 (14 blood samples) - One predose blood sample was collected and 13 blood samples were collected after the last dose of LTG extended-release at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours (the next morning prior to the first dose of LTG-IR)
• Day of Conversion back to IR: Day 29/30 (20 blood samples) - The first dose of the new LTG-IR regimen was taken; postdose samples were collected at: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours; the second dose of LTG-IR was taken just after the 12-hour sample; and postdose samples were collected at 12.5, 13, 13.5, 14, 15, 16, 18,

20, 22 and 24 hours (the next morning, before the morning LTG-IR dose for Day 30).

Concomitant AED trough levels were collected at the same time as the predose samples on Days 13 and 14 immediately prior to the subject's AM doses.

Serum samples were assayed for lamotrigine using a method based upon solid phase extraction followed by LC/MS/MS employing positive-ion Turbo Ion Spray ionization (lower limit of quantification (LLQ) 4.00 ng/mL).

Study LEP103944: Serum concentrations of lamotrigine in QC samples			
	Nominal Concentrations		
	QC 1	QC 2	QC 3
	15.00 ng/mL	350.00 ng/mL	3500.00 ng/mL
Overall Mean	15.17	354.57	3515.71
S.D.(within run means)	0.47	6.60	77.34
Precision(%CV)	3.1	1.9	2.2
Average Bias %	1.1	1.3	0.4
n	86	88	88
Average Within Run Precision (%)	2.9	1.4	1.6
Between Run Precision (%)	1.0	1.2	1.5

Number of subjects:
Forty-five subjects (15 subjects per dosing group, 25M and 19F) were to be enrolled in this study in order to obtain 36 subjects (12 subjects per dosing group) who completed the study. A total of 44 subjects were enrolled in the study;
15 in Group 1 (Neutral),
15 in Group 2 (Induced),
14 in Group 3 (Inhibited).

Thirty-eight subjects completed the Baseline Phase (Phase 1) and 35 subjects completed the Extended-release Treatment Phase (Phase 2) and the IR Phase (Phase 3).

Male or female subjects ≥13 years of age with a confident diagnosis of epilepsy >24 weeks prior to Screen, and currently being treated with a stable regimen of LTG-IR and up to two additional concomitant AEDs, for at least four weeks prior to Screen, were eligible for entry into the study.

Treatment administration:
Subjects remained on their current twice daily LTG dose, but were switched to LTG-IR study drug at Screen. After two weeks of baseline treatment, they were switched to once daily LTG extended-release study drug at Visit 3, and remained at the same total daily dose. After two weeks on the once daily LTG extended-release formulation, subjects returned to the site for another visit (Visit 5), and were switched back to twice daily LTG-IR study drug for one week. At the end of the week, subjects came in for their End of Study (EOS) visit and completed the study. At the EOS visit, subjects were switched back to commercially available twice daily LAMICTAL.

Subjects were instructed to take their study drug at the same time each day, with a maximum deviation of ±1 hour around their daily dosage time/s

The average doses in this study is given in the following Table:

		Average Dose of LAMICTAL (mg)			
Dosing Group	n	Mean	Median	Min	Max
Group 1: Neutral	15	363.3	400.0	200	600
Group 2: Induced	15	550.0	600.0	200	1200
Group 3: Inhibited	14	282.1	200.0	50	800

Criteria for evaluation:

PK parameters were calculated for each subject on Days 14, 15, 28 and 29:
The primary endpoints were: steady state AUC(0-24), Cmax and Cτ of LTG.
The secondary endpoints were: 1) Tmax and fluctuation index of LTG; 2) adverse events (AEs) and changes in blood pressure and heart rate; 3) change in seizure frequency during each of the study phases; and 4) subject preference at End of Baseline and Extended-Release Treatment Phases.

Efficacy analyses included seizure counts, changes in seizure frequency, the investigator's assessment of seizure frequency, and the subject preference questionnaire.

Pharmacokinetic Results:

The achievement of steady-state for both IR and extended-release regimens was assessed with mixed effect model. A summary of the analysis results is presented in the Table below. Steady-state is statistically confirmed if both the slope and associated 90% CI fall within the range of 0.91 to 1.10. Therefore, for the extended-release formulation, achievement of steady-state was statistically confirmed following 14 days of once daily dosing. For the IR formulation, since the lower boundary of the 90% CI fell slightly outside the prescribed threshold, the achievement of steady-state was assumed to have occurred by the sponsor following 14 days of BID administration.

Table: Statistical Summary of Serum LTG Steady State Assessment

Serum LTG PK Parameter	Treatment	Slope (90% CI)
Cτ	LTG-IR	0.94 (0.90, 0.98)
Cτ	LTG-XR	0.96 (0.93, 1.01)

PK parameters are presented by AED group in the following Tables for induced, inhibited and neutral concomitant AED therapy. High variability was observed in the data.

Table: Summary of Selected Serum LTG Pharmacokinetic Parameters - AED Group=Induced

Treatment	Day	N	AUC(0-24)[1] (ng.h/mL)	Cmax[1] (ng/mL)	Cmin[1] (ng/mL)	Fluctuation Index[2]	Tmax (h)[3]
LTG-IR	14	12	100369 (85.9%)	6709 (80.5%)	2655 (100%)	0.986 (40.1%)	1.01 (0.50-2.98)
LTG-XR	15	11[4]	92026 (75.9%)	5488 (64.1%)	2509 (79.1%)	0.780 (31%)	6.00 (0.00-23.85)
LTG-XR	28	12	78963 (100%)	4767 (85.9%)	2095 (131%)	0.817 (50.0%)	4.00 (0.00-24.00)
LTG-IR	29	12	102585 (94.0%)	6500 (83.1%)	2158 (144%)	0.994 (38.4%)	1.49 (0.50-3.92)

Source Data: Table 9.12 and Table 9.14

1. geometric mean (CV%)
2. arithmetic mean (CV%)
3. median (min-max)
4. Subject 15 Day 15 parameters excluded

Table: Summary of Selected Serum LTG Pharmacokinetic Parameters - AED Group=Inhibited

Treatment	Day	N	AUC(0-24)[1] (ng.h/mL)	Cmax[1] (ng/mL)	Cmin[1] (ng/mL)	Fluctuation Index[2]	Tmax (h)[3]
LTG-IR	14	12	207853 (59.7%)	10224 (57.5%)	7435 (53.9%)	0.318 (27.0%)	1.00 (0.50-6.13)
LTG-XR	15	12	198012 (62.8%)	9369 (58.3%)	7409 (57.6%)	0.240 (44.3%)	9.08 (2.88-24.00)
LTG-XR	28	10	167246 (48.1%)	7769 (49.0%)	6316 (47.1%)	0.209 (16.4%)	11.00 (0.00-24.00)
LTG-IR	29	10	175064 (45.5%)	8571 (46.5%)	6126 (49.6%)	0.334 (37.0%)	1.48 (0.40-9.83)

Table: Summary of Selected Serum LTG Pharmacokinetic Parameters - AED Group=Neutral

Treatment	Day	N	AUC(0-24)[1] (ng.h/mL)	Cmax[1] (ng/mL)	Cmin[1] (ng/mL)	Fluctuation Index[2]	Tmax (h)[3]
LTG-IR	14	14	141949 (43.4%)	7816 (39.3%)	4570 (46.6%)	0.545 (29.5%)	1.50 (0.50-3.02)
LTG-XR	15	13	114369 (44.3%)	5802 (38.7%)	3314 (66.4%)	0.470 (62.2%)	10.00 (0.00-24.00)
LTG-XR	28	13	138424 (40.8%)	6831 (38.6%)	4873 (41.0%)	0.341 (40.6%)	6.00 (0.00-24.00)
LTG-IR	29	13	152454 (44.0%)	8266 (40.0%)	4970 (49.9%)	0.518 (27.2%)	1.00 (0.48-2.00)

These tables suggest that in the Induced group the mean exposures are lower after the administration of ER tablets, which tend to revert back after the administration of the IR tablets. Subjects on neutrals and inhibitors tended to have minimal differences in exposure all through the study. Individual subject data will be discussed in the following sections.

Relative Bioavailability Comparisons

Extended Release (Day 28) vs IR (Day 14)

An assessment of the relative bioavailability of LTG at steady-state of the extended release on conversion from the IR at steady-state (Day 28 vs Day 14) was conducted by the sponsor using analysis of variance (ANOVA). A summary of the analysis results is presented in the following Table:

Table: Statistical Summary of relative bioavailability analysis of serum LTG Steady State PK Parameters – Day 28 vs Day 14

Serum LTG PK Parameter	AED Group	Geometric LS Mean Ratio Extended Release (Day 28) / IR (Day 14)	90% CI
AUC(0-24)	Overall	0.90	0.832, 0.973
	Induced	0.79	0.688, 0.899
	Inhibited	0.92	0.798, 1.067
	Neutral	1.00	0.884, 1.141
Cmax	Overall	0.82	0.749, 0.890
	Induced	0.71	0.614, 0.822
	Inhibited	0.86	0.733, 1.008
	Neutral	0.89	0.775, 1.026
C_τ	Overall	1.03	0.973, 1.095
	Induced	0.99	0.893, 1.093
	Inhibited	0.98	0.878, 1.093
	Neutral	1.14	1.033, 1.252

- The relative bioavailability based on dose normalized AUC(0-24) following conversion from IR to extended-release at steady-state was estimated to be 90%

- For patients taking the induced AED, however, lower extent of LTG systemic exposure was observed with the extended-release (estimated ratio for AUC(0-24): 0.79 (90% CI: 0.688-0.899), and for Cmax: 0.71 (90% CI: 0.614-0.822)) than the IR reference formulation.

- For patients taking neutral AED, extent of differences between the extended-release and IR formulations extent of LTG systemic exposure were minimal

- For patients taking the inhibited AED, extent of differences between the extended-release and IR formulations of LTG systemic exposure were also minimal

- In all three AED groups, similar steady-state trough concentrations were observed on attainment of steady-state for the extended-release (Day 28) in comparison to the IR (Day 14).

Due to the large variation in doses administered within each AED group, a dose normalized analysis of relative bioavailability assessment for AUC(0-24), Cmax and Cτ values (normalized by total daily doses) was performed overall and by AED group and results obtained were similar to the analysis without dose normalization.

Table: Statistical Summary of Serum LTG Steady State PK Parameters – Day 28 vs Day 14

Serum LTG PK Parameter	AED Group	Geometric LS Mean Ratio Extended Release (Day 28) / IR (Day 14)	90% CI
AUC(0-24) / Total Daily Dose	Overall	0.90	0.836, 0.978
	Induced	0.79	0.688, 0.899
	Inhibited	0.94	0.810, 1.084
	Neutral	1.00	0.882, 1.140
Cmax / Total Daily Dose	Overall	0.82	0.755, 0.896
	Induced	0.71	0.613, 0.823
	Inhibited	0.88	0.750, 1.030
	Neutral	0.89	0.775, 1.026
Cτ / Total Daily Dose	Overall	1.04	0.976, 1.098
	Induced	0.99	0.894, 1.094
	Inhibited	0.99	0.884, 1.101
	Neutral	1.14	1.033, 1.252

Source Data: Table 9.22 and Table 9.23
LS means refer to Day 14 of each treatment
Individual values analysed are divided by Total Daily Dose (mg)
Geometric means here are model-based Adjusted LS Means (for the details of the model see Section 5.8.10)

The individual subject data for this comparison is given in the following Tables for the three groups:

Subjects on Neutrals:

	AUC(0-24)					Cmax				
	Day 14 IR	**Day 28 MR**	**Day 29 IR**	**D28: D14**	**D29: D14**	**Day14 IR**	**Day 28 MR**	**Day 29 IR**	**D28: D14**	**D29: D14**
111	136877	180763	197883	132.06	144.6	(b) (4)				
1	254018	209440	260442	82.45	102.5					
12	73096.9	59789.2	75606.6	81.79	103.4					
13	219863	220203	237009	100.15	107.8					
14	69614.2	84271.8	73218.2	121.06	105.2					
17	229475	168813	265443	73.56	115.7					
18	130368	119396	158927	91.58	121.9					
19	111497	98316.3	97566.2	88.18	87.5					
20	148201	149417	160479	100.82	108.3					

						(b) (4)
21	161684	199475	172207	123.37	106.5	
23	88386.3	106150	136762	120.10	154.7	
24	169954	161359	156698	94.94	92.2	
27	132658	161216	145801	121.53	109.9	

In this group subjects had similar exposures with the IR and ER administration through out the study. One subject had about a 30% reduction in exposure, but this is within the 17-40% variability seen in other studies.

Subjects on Inducers:

	AUC(0-24)					Cmax				
	Day 14 IR	Day 28 MR	Day 29 IR	D28: D14	D29: D14	Day14 IR	Day 28 MR	Day 29 IR	D28: D14	D29: D14
161	70968	30586.3	45583	43.1	64.2	(b) (4)				
2	395234	400136	451903	101.2	114.3					
3	162990	48673.3	117056	29.9	71.8					
4	42888	31677.1	54535.1	73.9	127.2					
151	194602	156875	223830	80.6	115.0					
174	161465	157079	204341	97.3	126.6					
31	81083	83765	89265.2	103.3	110.1					
32	116246	107155	108114	92.2	93.0					
35	119440	117685	119730	98.5	100.2					
36	126046	117293	162122	93.1	128.6					
11	39363	28099	34623.2	71.4	88.0					
15	30370	36295.3	34819.4	119.5	114.6					

In subjects on inducers, TWO subjects had about a 57-70% reduction in the AUC(0-24) The Cmaxs in this group showed a reduction of 45-77% in THREE subjects. These subjects again had an increase in exposure on converting back to the IR group on Day 29.

Subjects on Inhibitors:

	AUC(0-24)					Cmax				
	Day 14 IR	Day 28 MR	Day 29 IR	D28: D14	D29: D14	Day14 IR	Day 28 MR	Day 29 IR	D28: D14	D29: D14
113	382913					(b) (4)				
115	140960	126591	141951	89.8	100.7					
51	204509	215904	202997	105.6	99.3					
53	212322	228537	210473	107.6	99.1					
54	148591	161767	154054	108.9	103.7					
171	162958	120061	159366	73.7	97.8					
172	192437	164085	179152	85.3	93.1					
33	64638	69062.3	69646.4	106.8	107.7					
34	399834	382333	399255	95.6	99.9					
26	522652	155417	170562	29.7	32.6					
29	196994	209595	213703	106.4	108.5					

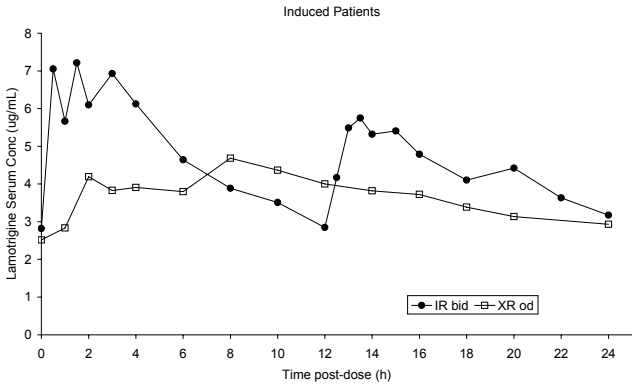
30	223759		141951	89.8	100.7	(b) (4)

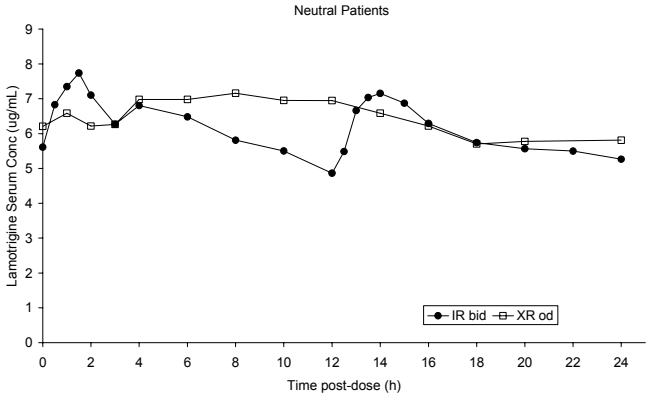
ONE subject had about a 70% reduction in exposure to lamotrigine on coversion to the ER group, although this subject also had lower exposure when converted back to the IR group. This reduction could have occurred for some unknown reasons. The exposures in rest of the subjects were similar throughout the study in either treatments.

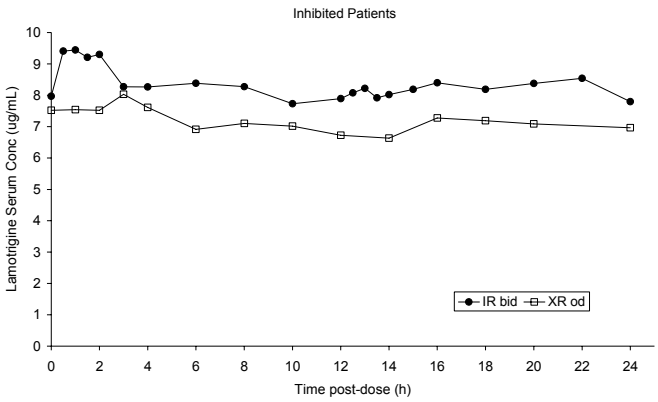
This shows that some subjects in each of mainly the Induced group may not have similar therapeutic responses.

Median Serum concentration time profiles are given in the following Figures:

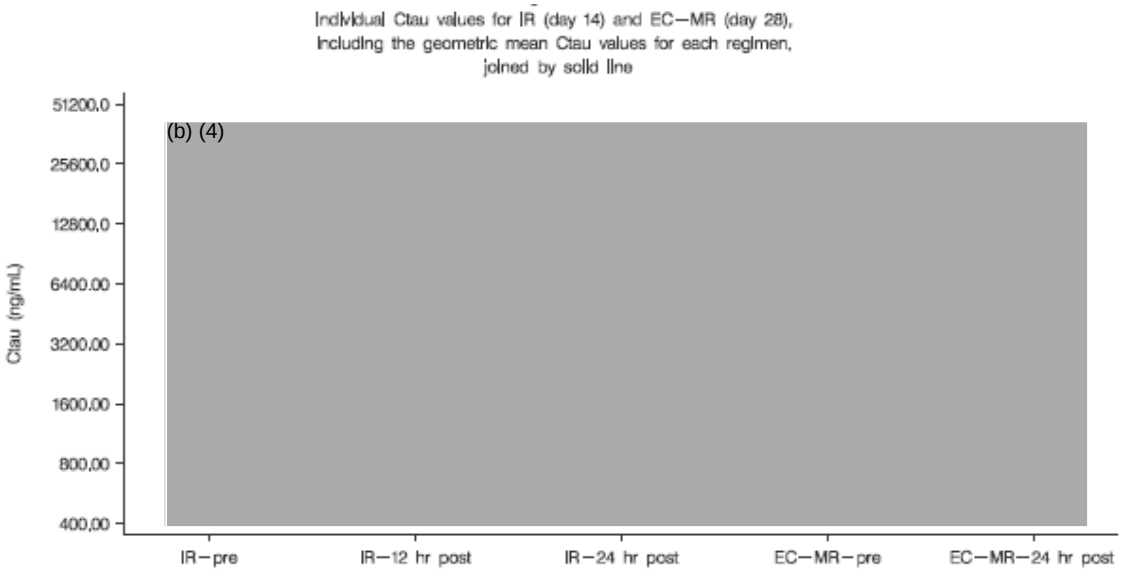
Figure **Median Serum Lamotrigine Concentration-Time Profiles for Steady-State IR and Steady State XR for each AED Group**







Individual parameter comparisons for the IR and ER are shown in the following Figure:



Extended Release (Day 15) vs IR (Day 14)

Systemic exposure following immediate conversion from the IR to extended-release formulation on Day 15 was assessed using ANOVA. A summary of the analysis results with dose normalization is also presented below.

Table: Statistical Summary of Serum LTG PK Parameters – Day 15 vs Day 14

Serum LTG PK Parameter	AED Group	Geometric LS Mean Ratio Extended Release (Day 15) / IR (Day 14)	90% CI
AUC(0-24) / Total Daily Dose	Overall	0.87	0.827, 0.908
	Induced	0.82	0.759, 0.896
	Inhibited	0.95	0.874, 1.032
	Neutral	0.83	0.770, 0.897
Cmax / Total Daily Dose	Overall	0.80	0.763, 0.837
	Induced	0.73	0.675, 0.799
	Inhibited	0.92	0.845, 0.993
	Neutral	0.76	0.702, 0.820

Source Data: Table 9.26 and Table 9.27
LS mean Test=Day 1 of XR dosing (Day 15), Reference=Day 14 of IR dosing
Individual values analyzed are divided by Total Daily Dose (mg)

Immediately following the conversion to the extended-release formulation on Day 15, the relative bioavailability based on dose normalized AUC(0-24) was estimated to be 87% (90% CI: 82.7%-90.8%) overall and ranged from 82% to 95% among the AED groups.

On immediate conversion from IR at steady-state to the extended-release formulation, a reduction in the relative bioavailability in terms of AUC(0-24) was observed, with a LS adjusted mean decrease of 17% in neutral subjects, 18% in subjects on induced AED therapy, and 5% in subjects on inhibiting AED therapy.

There was a reduction in dose normalized Cmax in all three AED groups. There was a mean decrease of in Cmax of 8% in subjects who were taking inhibiting AEDs, 24% in neutrals and 27% in subjects taking enzyme inducing AEDs.

The individual data for the 3 groups is given in the following Table along with the individual ratios for MR/IR for AUC and Cmax:

Subjects on Neutrals:

Table: Individual subjects AUC(0-24) for the IR (Day 14) and MR (Day 15):

	AUC (0-24)			Cmax		
ID	Day 14 IR	Day 15 MR	MR/IR Ratio as %	Day 14 IR	Day 15 MR	MR/IR Ratio as %
111	136877	111244	81.27	(b) (4)		
1	254018	210870	83.01			
12	73096.9	49378	67.55			
13	219863	159893	72.72			
14	69614.2	59533.3	85.52			
17	229475	162779	70.94			
18	130368	123725	94.90			
19	111497	109391	98.11			
20	148201	148274	100.05			
21	161684	112273	69.44			
23	88386.3	72141.7	81.62			
24	169954	160442	94.40			
27	132658	122384	92.26			

This shows that immediately upon conversion there were FOUR subjects that had about 27-33% reduction in the exposure of lamotrigine when on neutral antiepileptic.

Regarding Cmax as well, there were FOUR subjects that had about 32% reduction in Cmax immediately upon switching to the ER dosage form. These were within the variability of lamotrigine in general.

Subjects on Inducers:

Table: Individual subjects AUC(0-24) for the IR (Day 14) and MR (Day 15):

	AUC (0-24)			Cmax		
ID	Day 14 IR	Day 15 MR	MR/IR Ratio as%	Day 14 IR	Day 15 MR	MR/IR Ratio as %
161	70968.8	61420	86.55	(b) (4)		
2	395234	370065	93.63			
3	162990	78121.5	47.93			
4	42888.8	29641.9	69.11			
151	194602	163358	83.94			
174	161465	98227.9	60.84			
31	81083.9	79067.7	97.51			
32	116246	94971.3	81.70			
35	119440	118449	99.17			
36	126046	126858	100.64			
11	39363.3	42068.7	106.87			
15	30370.4	31763.3	104.59			

In the group on inducers there were ONE subject that had about 53% reduction in the exposure to lamotrigine ER immediately upon switching.

In this group there were TWO subjects that had 47-61% reduction in Cmax immediately after switching and ONE subject had a 3-fold higher Cmax.

Subjects on Inhibitors:

Table: Individual subjects AUC(0-24) for the IR (Day 14) and MR (Day 15):

	AUC			Cmax		
ID	Day 14 IR	Day 15 MR	MR/IR Ratio	Day 14 IR	Day 15 MR	MR/IR Ratio
113	382913	386230	100.87	(b) (4)		
115	140960	134071	95.11			
51	204509	-	-			
53	212322	204337	96.24			
54	148591	147526	99.28			
171	162958	148778	91.30			
172	192437	188754	98.09			
33	64637.5	59457.3	91.99			
34	399834	366364	91.63			
26	522652	459483	87.91			
29	196994	185692	94.26			
30	223759	225210	100.65			

In the subjects on inhibitors no appreciable change in exposure was obtained immediately after switching.

The maximum reduction in Cmax obtained in this group was 14%

Efficacy Analyses

Due to the small number of subjects and the open-label design the study was not powered as an efficacy study.

Efficacy analyses were performed using the Safety Population. Average weekly seizure frequency was computed for each subject. For subjects who withdrew from the study, seizure data was averaged for the portion of the study the subject completed up to the time of study drug discontinuation.

Seizure counts

The number of seizures and the change in seizure frequency (absolute change and percent change from Historical Baseline) were computed for each subject during each study phase. The mean, median, standard deviation, minimum, and maximum were summarized.

During each treatment phase, there was no change in the median weekly seizure frequency.

Seizure Type	Period	Group	n	Mean	SD	Median	Min.	Max
All Seizures	Entire Tmt Period	Screen	40	0.8	2.51	0.0	0	14
		Phase 1/IR	44	1.8	6.33	0.0	0	36
		Phase 2/XR	38	1.4	3.93	0.0	0	22
		Phase 3/IR	35	1.5	5.77	0.0	0	32

Subject Preference Questionnaire

The subject preference questionnaire was summarized by frequency distributions at each time point taken and compared between LTG-IR and LTG extended-release.

Approximately half of the subjects (54% at the end of the Extended-release Phase and 53% at the end of the IR Phase) indicated that they strongly preferred the once a day regimen.

Conclusions:

- Based on adjusted LS mean ratios, a similar LTG steady-state total daily exposure, AUC(0-24), was observed in subjects on neutral and inhibiting AEDs following attainment of steady-state with the extended-release formulation in comparison to the IR formulation. A mean decrease of approximately 21% in steady-state AUC(0-24) in subjects on concomitant enzyme inducing AEDs was observed, although some subjects in this group (Induced) showed a 57-70% decrease in exposure as well.
- A reduction in Cmax of the extended-release formulation at steady-state in comparison to the IR formulation was observed, ranging from a mean decrease of 11% in neutral subjects to a mean decrease of 29% in induced subjects
- Comparable steady-state trough concentrations for the extended-release formulation in comparison to the IR formulation were observed, with adjusted LS mean ratios close to unity, regardless of concomitant AED therapy.
- Compared to the IR formulation at steady-state, the mean fluctuation index was moderately reduced by approximately 17% to 37% among the three AED groups following the conversion to the extended-release formulation on attainment of steady-state.
- On immediate conversion from IR at steady-state to the extended-release formulation, a reduction in the relative bioavailability in terms of AUC(0-24) was observed, with a LS adjusted mean decrease of 17% in neutral subjects, 18% in subjects on induced AED therapy, and 5% in subjects on inhibiting AED therapy.
- Steady-state was statistically confirmed following 14 days of once daily dosing of LTG extended-release regimen. Achievement of steady-state was assumed following 14 days of BID dosing of LTG-IR regimen.

SUPPORTIVE POPULATION PK AND PK-PD ANALYSES

(Phase II and III Study)

Note: These analyses have been evaluated by Dr. Joga Gobburu.

Title: ***Population PK and PK-PD Analyses of Lamotrigine XR in Patients with Partial Seizures Using Data from LAM100034 and LEP103944***

Population PK and PK/PD Objective

The objectives of this pooled PK and PKPD modeling analysis are:

- To describe the PK profile of the XR formulation in the target population.
- To investigate sources of variability in the pharmacokinetics of lamotrigine
- To describe the relationship between exposure and formulation.
- To describe the relationship between seizure frequency and exposure to lamotrigine after XR administration.
- To investigate the effect of changing formulation and dosing regimen (XR vs IR) on efficacy parameters.

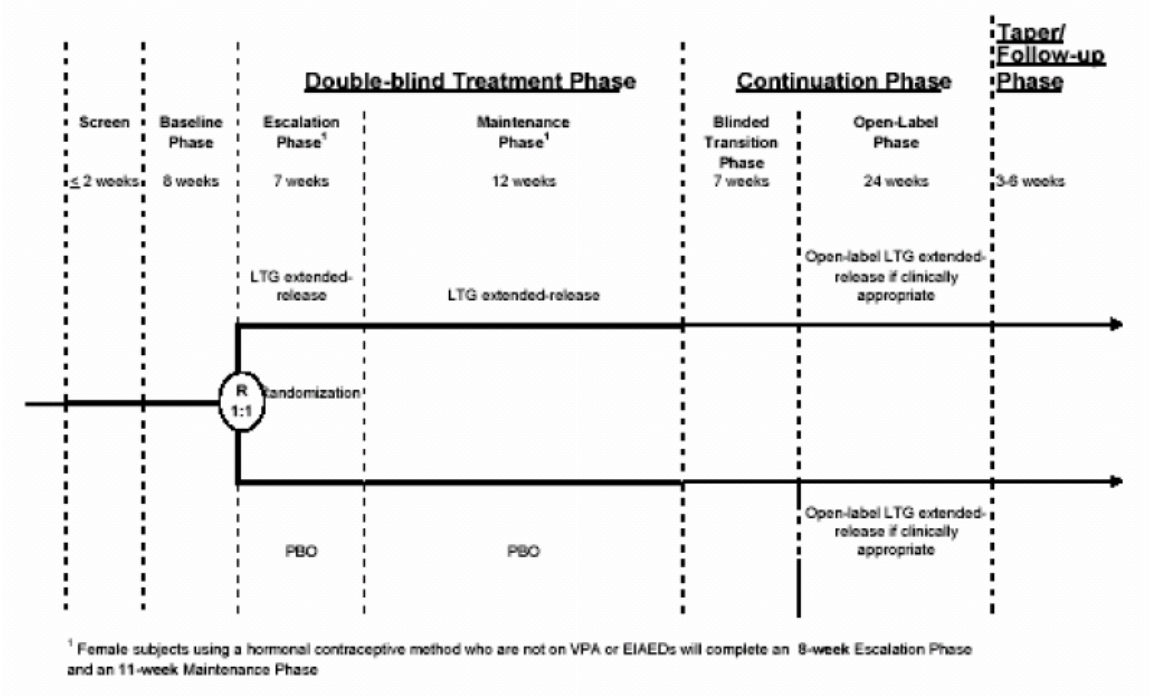
Study Endpoints

In study LAM100034, the primary endpoint was the Percent change from Baseline in partial seizure frequency during the entire Double-Blind Treatment Phase; a secondary endpoint was serum concentrations of lamotrigine collected to evaluate population pharmacokinetic parameters for lamotrigine.

In study LEP103944, the primary endpoints were steady state $AUC_{24\text{-}SS}$, $C_{max\text{-}SS}$ and $C_{min\text{-}SS}$ of lamotrigine, secondary endpoints included change in seizure frequency during each of the study phases.

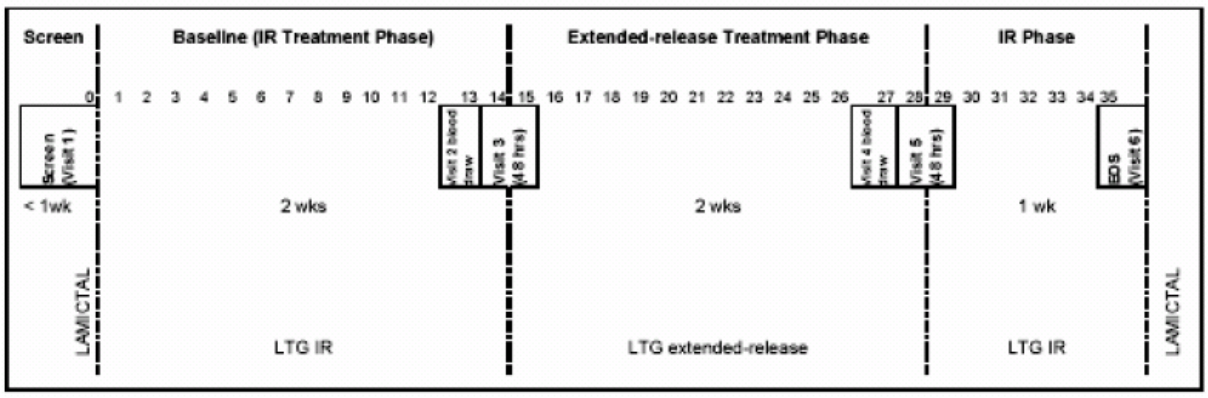
Study Design of the two studies

LAM100034 was an international, multicenter, double-blind, randomized, placebo controlled, parallel-group study in four phases after screening: Baseline, Double-Blind Treatment, Continuation, and Taper/Follow-up phase.



Note: The open label phase was 45 weeks as opposed to 24 weeks shown in the schematic above

LEP103944 was an open-label, multicenter, double-conversion study in three phases after screening: a baseline with lamotrigine IR, a treatment phase with lamotrigine XR and a last phase with lamotrigine IR.



Number of Subjects:

PK Analysis:
The pharmacokinetic population included 144 subjects treated with lamotrigine

Efficacy Analysis:
---The efficacy population included all subjects included in the PK population and subjects treated with placebo in study LAM100034, i.e. a total of 264 subjects
---The second analysis conducted on a subset of the data (ignoring imputed values of

seizure frequency) included 233 subjects, only 15 from study LEP103944
---LAM100034 efficacy population included all subjects included in the PK population and subjects treated with placebo, i.e. a total of 223 subjects.
---The analysis of the percentage change from baseline and of response data included 216 subjects, all belonging to study LAM100034
---The analysis of relationship between exposure and occurrence of adverse events used the complete population of 264 subjects included in the primary efficacy analysis

	Placebo LAM100034	Lamotrigine IR/ER LEP103944	Lamotrigine ER LAM100034
Number of Subjects included in pharmacokinetic/pharmacodynamic/biomarker analysis:	121	41	102
Adults (include range from protocol here):	112	41	95
Pediatrics (include range from protocol): 13-18yr	9	0	7
Sex			
Female:	58	25	57
Male:	63	16	45
Ethnicity			
Hispanic or Latino:	na	na	na
Not Hispanic or Latino:			
Race			
African American/African Heritage:	10	1	2
American Indian or Alaskan Native:	2	0	2
Asian – East Asian Heritage:			
Asian – central/south Asian Heritage:	9		15
Asian –East Asian Heritage:	14	0	13
Native Hawaiian or Other Pacific Islander:			
White – Arabic/North African Heritage:			
White – White/Caucasian/European Heritage:	83	39	69
mixed race	1	0	0

PK Measurements in the studies:

LAM100034

- At least four, up to six blood samples per subject.
- During the maintenance phase at visits 6, 7 and 8 (treatment weeks 11, 15 and 19)

The date and time these subjects took their last study drug dose prior to discontinuation was to be recorded in the CRF. The date and time of doses taken for the seven days prior to the PK sampling visits was to be recorded in the seizure diary as well as any missed doses.

LEP103944

- 70 blood samples collected by subject.
- Visit 2 (Day 13): predose sample.

- Visit 3

Days 14 and 15: (21 blood samples): Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 22 hours after last two IR doses
Day 15 and 16 (13 blood samples): pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours after 1st XR dose.

- Visit 4, Day 27 predose sample
- Visit 5

Days 28 and 29 (14 blood samples): Predose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 hours, last XR dose
Days 29 and 30 (20 blood samples): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 22 and 24 hours, IR doses.

Efficacy Assessments in the studies

LAM100034:
Daily diary were used to collect seizure count. Daily seizure frequency was derived by GSK and reported in the analysis dataset at visits corresponding to baseline, week 3 and 7 (during escalation), and weeks 11, 15 and 19 during maintenance phase.

LEP103944:
A 2-week seizure count was collected and daily seizure frequency derived during lamotrigine IR treatment phase and during lamotrigine XR treatment phase. Seizure frequency was also derived and reported on the first day of the switch from IR to XR and from XR to IR.

Safety Assessments in the studies:

Safety assessments were made all through the Studies

Population PK Analysis Methodology:

The population PK and PKPD analyses are based on multiple regression using non linear mixed effect models. A structural model was built first, including error models. Then covariates were added as necessary, using a predefined strategy.

- A one-compartment disposition model with first or zero order absorption processes was explored.
- Clearance and volume of distribution were scaled for body weight using the typical allometric exponent of 0.75 for clearance and 1 for volume as follows:
- CL= THETA(x)*(WEIG/MWEI)**0.75 and V=THETA(y)*(WEIG/MWEI) where WEIG is the individual's weight and MWEI is the median weight in the population.
- Between-subjects variance was investigated on all PK parameters.
- The effect of dose was investigated on bioavailability, on absorption parameters (rate, rate constant, duration) and on clearance for information.
    - Study effects on clearance and F were assessed. Lamotrigine is known to induce its own metabolism. Since subjects were already treated with lamotrigine in study LEP103944, clearance or F may differ between studies.

- The effect of PK occasion (IOV) was estimated since the rich PK profiles collected in the switch study showed large variability between the day of observation.
- Since dosing regimen and formulation are confounded, the effect of formulation (IR/XR)/regimen (BID/QD) was investigated on the relative bioavailability and the absorption rate parameters.
- Since lamotrigine was administered up to 133 days, the effect of number of study treatment days was investigated on apparent CL (de-induction during prolonged administration of lamotrigine).

Covariates for population PK analysis

i. The effect of demographic factors such as age, sex and race, were explored on clearance and volume: age was investigated on clearance and volume.
ii. The effect of disease on the pharmacokinetics of XR lamotrigine (apparent CL and V) was investigated based on the average baseline daily seizure frequency collected over 28 days.
iii. The relationship of clearance with kidney function, using estimates of clearance of creatinine.
iv. The relationship of PK with liver function using the hepatic laboratory values: ASAT, ALAT, alkaline phosphatases (AP) and total bilirubin, using dichotomised variables: greater than median of the data, or greater than 2.5*upper limits of normal range

Exposure-response analysis methodology:

The exposure-response model development used the FOCE method in NONMEM for continuous variables (log-transform seizure frequency).

The exposure-response model development used the FOCE method with likelihood and numerical options in NONMEM for categorical variable responders/nonresponders.

Seizure frequency**:** Due to the different study design, the percentage change in seizure frequency was available only in study LAM100034, therefore the primary analysis used the seizure frequency rather than its change from baseline.

The model to predict the pharmacodynamic endpoint (i.e. seizure frequency) was a function of a "baseline" or intercept, placebo, time, lamotrigine exposure, and concomitant AEDs effects. Each component of the model (i.e. placebo/time, lamotrigine, AED effects) was evaluated using linear, log-linear and saturable (E_{max} model) effects: the simpler, more robust model was selected when several applied with the same objective function.

The effect of time in the study, expressed as days of treatment, was investigated as part of the base model. The models evaluated include: a constant placebo effect throughout the study, proportional to number of days, proportional to number of Log_e of days, and a saturable model.

A proportional error and a constant additive error models were evaluated for the residual error of the PKPD models.
Between-subject random effects were explored on all parameters. Additive or exponential models were tested.
The effect of the following covariates was investigated:

- Demographic data: age, race and sex on intercept, placebo, and drug effects.
- AED concentrations or presence/absence on intercept, placebo time effect and lamotrigine effect.
- Lamotrigine regimen/formulation on drug effect.
- Study on drug effect and intercept

Percentage of change from baseline A subset of the data was used to analyze the percentage change from baseline (PCT):

- Only study LAM100034 was used because most of baseline values in LEP103944 were zero;
- Only subjects in LAM100034 with baseline seizure frequency >0.
- Because the distribution of the percentage change in seizure frequency was not normal, or log normal, the dependent variable used for the modeling was the rank of PCT, 1 being the smallest change (in fact an increase in seizure frequency).

Exposure-response analysis: "probability of response": Several criteria were chosen in the protocol to describe a responder. For the current analysis, the response variable was a dichotomized variable: subjects were qualified as having a positive response (RESP=1) when the number of seizures decreased by 50% or more from the baseline at any time point. This means that a subject could have a positive "response" at one visit, and later a negative response, depending on the frequency of seizure reported at that visit. This definition differs from the study LAM100034 analysis

Non linear mixed effect modeling was used to fit the likelihood of response. The logit of the probability of response was a function of a baseline, an effect of placebo treatment and of time which cannot be distinguished, and the effect of lamotrigine exposure. The usual residual plots of residuals can not be used in that case, since the dependent variable is the response 0 or 1 while the prediction PRED is the likelihood of response DV=0 or 1. Therefore, the population prediction of response 1 (PRED if DV=1, (1-PRED) if DV=0) and the individual prediction IPRED were compared to the proportion of observations RESP=1.

Results:

Pharmacokinetics:

The final model includes the effect of body weight on clearance and volume, the effect of concomitant administration of valproate (inhibitor) and of enzyme inducer AED and an effect of the study on the relative bioavailability.

Lamotrigine PK parameters from the final model is given below:

Symbol	Description	Est value	s.e.	95% CI	IIV in %
θ_1	CL	3.5	0.384	[2.75 ; 4.25]	
θ_2	VAL ON CL	-1.22	0.222	[-1.66 ; -0.785]	
θ_3	INU ON CL	1.73	0.486	[0.777 ; 2.68]	
θ_4	V	396	122	[156.7 ; 635.1]	
θ_5	KA IR	0.604	0.0576	[0.491 ; 0.717]	
θ_6	KA XR	0.105	0.0163	[0.073 ; 0.137]	
θ_7	STUDY on F	2.28	0.247	[1.80 ; 2.76]	
ω^2_1	IIV KA XR LEP	29.4	21.3	[-12.348 ; 71.148]	542.2
ω^2_2	IOV KA XR LEP	43.7	29.2	[-13.532 ; 100.932]	661.1
ω^2_4	IIV CL	0.706	0.186	[0.341 ; 1.071]	84.0
ω^2_5	IOV CL	1.63	0.8.38	[-0.012 ; 3.272]	127.7
ω^2_7	IIV KA IR	82.6	60.1	[-35.196 ; 200.396]	909
ω^2_8	IIV KA XR LAM	8.01	7.70	[-7.082 ; 23.102]	283.0
σ^2	PROP	2.43E-02	5.69E-03	[0.013 ; 0.035]	15.6
σ^2	ADD	4.71E-02	1.55E-02	[0.017 ; 0.077]	SD 0.217 µg/mL

Overall, 2786 lamotrigine concentrations were analysed. Lamotrigine pharmacokinetics was described by a one-compartment disposition PK model, with a first order absorption ($Ka=0.604h^{-1}$) for the IR tablet (study LEP103944) and with an apparent rate constant ($Ka=0.105h^{-1}$) for the XR formulation (LEP103944 and LAM100034).

The bioavailability of the XR formulation is not different from that of the IR formulation.

Clearance and volume of distribution were scaled for body weight using the typical allometric exponent of 0.75 for clearance and 1 for volume. After scaling, there was no difference in clearance and volume with age, sex or race/ethnicity.

The exposure was greater in LAM100034 than in LEP103944, the relative bioavailability $Frel_{LAM100034/LEP103944}$ was 2.28, which may be related to the populations included (naïve patients in LAM100034 and lamotrigine auto-induced patients in LEP103944).

With concomitant administration of inducers, CL/F in LAM100034 is predicted as (3.5+1.73)/2.28=2.29 L/h or in LEP103944: 3.5+1.73=5.23 L/h, which represent an increase of 49% compared to neutral AEDs.

With concomitant administration of valproate, CL/F in LAM100034 is predicted as (3.5-1.22)/2.28=1.0 L/h or in LEP103944: 3.5-1.22=2.28 L/h, which represent a decrease of 35% compared to neutral AEDs.

Co administration of other AEDs or benzodiazepines did not affect lamotrigine clearance.

Clearance was not influenced by laboratory markers of renal or liver function.

The inter subject variability on PK parameters is large, estimated as 80% on apparent CL and up to 200% on Ka from posterior estimates of individual parameters.

Reviewer's Comment: Overall the V and Ka calculation from this analyses seem inaccurate based on previous knowledge (sponsor acknowledges this in accuracy in the study report) and as such characterization of PK from this modeling does not lend much value and results should be viewed with caution

Exposure-response relationship with seizure frequency

The natural logarithm of total seizure frequency is described by the sum of an intercept (baseline frequency- prior to treatment initiation and at zero concentration of lamotrigine), the placebo effect with time in the study (a saturable "Emax" model) and a decrease proportional to lamotrigine concentrations.

The intercept (baseline) is larger for LAM100034 than in LEP103944.

The final model predicting the (Log_e of) total seizure frequency is the sum of an intercept, the shift for study LEP103944 (which had lower baseline seizure frequency), the effect of placebo/time and the lamotrigine effect (decrease proportional to Conc).

$$Log_e(\text{total seizure frequency}) = \theta_1 + \theta_2 * C + \theta_3 * nday/(\theta_4 + nday) + \theta_5 * LEP103944 + \theta_6 * baseline$$

Where nday is the number of treatment days since randomisation
C is the individual predicted lamotrigine concentration on the visit day
Baseline is the individual frequency (seizures/day)
θ_1 is the intercept of this equation
θ_2 is the population slope of concentration effect
θ_3 is the population maximum placebo/time effect
θ_4 is the number of days for half the maximum placebo/time effect
θ_5 is the shift of population intercept for study LEP103944 (lower frequency)
θ_6 is a contribution of the seizure frequency at baseline to the intercept.

On Day 0, before treatment, the initial seizure frequency is given by the sum: $[\theta_1 + \theta_5 + \theta_6 * baseline]$ for study LEP103944 and by $[\theta_1 + \theta_6 * baseline]$ for study

LAM100034.

The model parameters is given in the following Table:

Table: Population final PKPD model for Loge(total seizure frequency) complete population, N=264

	Description	Estimate	SEE	95% CI	IIV sd
θ_1	INTERCEPT	-1.17	0.219	[-1.599 ; -0.741]	
θ_2	SLOPE LAMOTRIGINE	-0.0452	0.0129	[-0.0705 ; -0.0199]	
θ_3	MAX DAY	-0.833	0.210	[-1.245 ; -0.421]	
θ_4	DAY50	18.1	8.20	[2.028 ; 34.172]	
θ_5	STUDY ON INTERCEPT	-1.43	0.176	[-1.77 ; -1.09]	
θ_6	BASELINE ON INT	0.470	0.114	[0.247 ; 0.693]	
ω^2_1		0.649	0.101	[0.451 ; 0.847]	0.806
ω^2_2		0.00528	0.0032	[-0.0010 ; 0.0116]	0.0727
σ^2_1		0.435	0.0418	[0.353 ; 0.517]	0.660

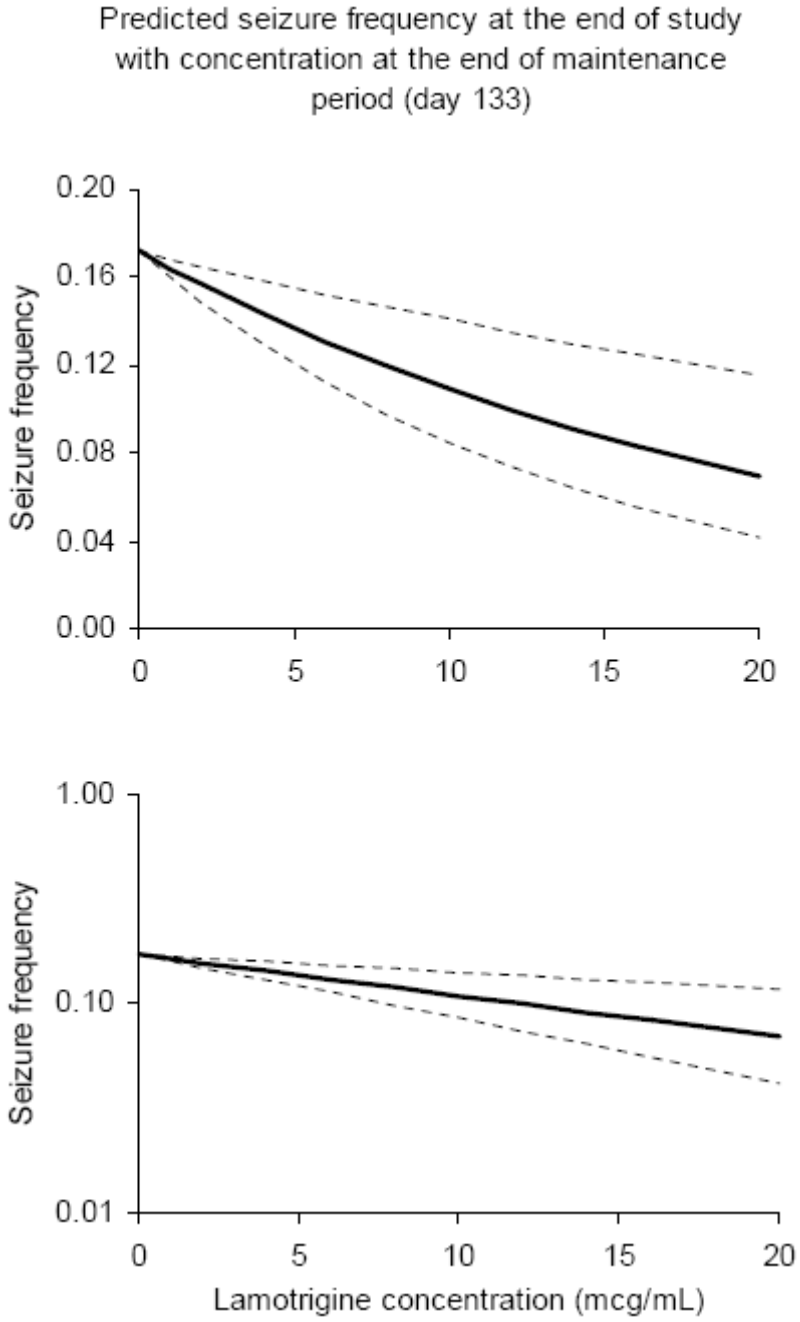
- Half the maximum effect of placebo/time is reached after 18 days treatment, it is not affected by age and sex.
- The resulting relationship leads to a population decrease in the loge of seizure frequency of 0.0452 decrease per µg/mL of lamotrigine serum concentration.
- The effect of lamotrigine on seizure frequency was not affected by concomitant AED, age or sex of the patients. The slope of effect of lamotrigine concentration does not differ between the two studies.
- There was no influence of formulation/dosing regimen on the slope of lamotrigine effect.

The relationship between seizure frequency and lamotrigine concentrations is presented in the following Figure. Predictions are made at the typical value of baseline (0.3 and 0 seizures for studies LAM100034 and LEP103944 respectively), at the end of the trial period (35 and 133 days respectively), and using the population parameter estimate for lamotrigine effect (dark lines) and at the limits of the 90 % confidence interval of parameter estimate for lamotrigine effect (thin dotted lines).

The top panel (linear plot) shows the predicted change between placebo treatment and maintenance lamotrigine concentration, illustrating the fact that the change is greater in subjects with larger baseline seizure frequency. The bottom panel (log-linear scale)

shows that the slope of concentration effect is identical whatever the baseline frequency.

Figure: Model predictions of the effect of lamotrigine concentrations



As the relationship between seizure frequency and lamotrigine serum concentration is linear with the loge of seizure frequency, patients with higher baseline seizure frequency will potentially benefit more, in terms of the total reduction in the number of seizures in comparison to a patient with a low number of seizures before treatment, with increasing lamotrigine serum concentrations.

It is likely that this concentration effect relationship is underestimated, as shown by a supplemental analysis of LAM100034 data alone. Moreover, this analysis has shown that the individual variability of this effect is negligible.

Almost all patients in LEP103944 had adequate seizure control prior to their participation in the study and had relatively constant lamotrigine concentration throughout the study. Effectively these patients only contributed data at the top of their individual concentration-response curve, with no information on the rest of their curves. This non-random data missingness would cause bias in the estimates of the model parameters. However, since the majority of the seizure frequency data were collected in LAM100034, the bias in the analysis using the combined data is expected to be minor.

Exposure-response relationship with probability of response

Response data were also derived from the frequency of seizures at baseline and during treatment for study LAM10034. A responder in this study was defined as a patient with a ≥ 50% reduction in seizure frequency from their pre-study baseline, for each separate double blind treatment phases. In the current analysis, a response was positive if at any visit, the patient with a ≥ 50% reduction in seizure frequency.

The logit of the probability of response is a linear function of an intercept (representing the probability at baseline of a response simply by chance), a disease model of placebo time effect (the probability of response increasing with time proportionally to the number of treatment days) and an increase proportional to predicted lamotrigine concentrations.

The logit model is the sum of a baseline, an effect of placebo/time and the lamotrigine effect (increase proportional to C).

$LP = \theta_1 + \theta_2 * C + \theta_3 * nday$

Where nday is the number of treatment days

C is the individual predicted lamotrigine concentration on the visit day

θ_1 is the population baseline, gives the probability of chance/placebo response

θ_2 is the population slope of lamotrigine concentration effect

θ_3 is the population slope of time effect (nday)

The probability of response for a given individual, at a time in the study and for a predicted concentration was obtained by the equation:

$P=X/(1+X)$

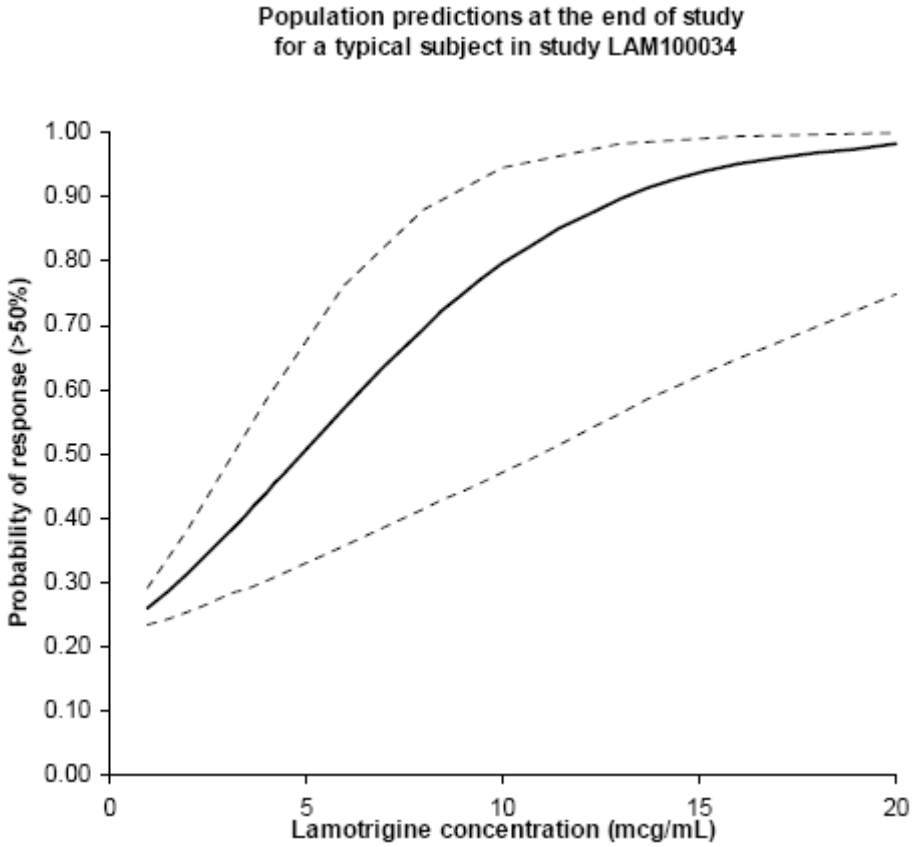
Where $X=\exp(LP+\eta)$

in which η is a random effect which represents the subject's difference to the population. When the observed response is 0, the variable to be fitted is Y=1-P; when the observation is 1, Y=P.

The following Figure represents the probability of response (change>50%). For each study, predictions are made at the typical value of logit intercept (which gives the probability of response by chance), at the end of the trial period (5 and 19 weeks

respectively), and using the population parameter estimate for slope of lamotrigine effect (dark lines) and at the limits of the 90 % confidence interval of parameter estimate for lamotrigine effect (thin dotted lines).

Figure: Model predictions of the effect of lamotrigine concentrations



The logistic regression analysis of response data showed an increase of the probability of response with increasing concentration.

The lamotrigine effect on probability of response was not affected by concomitant AED, and does not differ between the populations studied.

The concentration associated with a 50% probability of response was close to 5 µg/mL, the median maintenance concentration observed in LAM10034. This median concentration and range is associated with current IR total daily dosing recommendations for the various AED groups. Given the comparable bioavailability between the extended release formulation and the IR formulation given the same total daily dose in terms of both trough concentrations and total daily AUC, application of existing daily IR dosing recommendations for the XR formulation to yield a clinically significant reduction in seizure frequency can be supported.

Exposure-safety relationship with selected adverse events:

Nausea, ataxia, diplopia and dizziness occurrence were analyzed. The frequency of occurrence of these adverse events was too low for investigation of the exposure-response. No relationship could be established between adverse events and lamotrigine concentrations.

The adverse events in this population dataset is shown in the following Table:

Table: Summary of adverse events in the PK safety dataset (264 subjects, 1253 records).

AE		Placebo	Lamotrigine
Dizziness	N subjects	2	9
	N observations	4	24
Ataxia	N subjects	1	3
	N observations	2	3
Diplopia	N subjects	1	1
	N observations	3	1
Nausea	N subjects	1	3
	N observations	3	6

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ANALYTICAL VALIDATION

Summary of parameters for the full validation and abbreviated validation is given below. Small changes were made to the original assay to eliminate the concentration dry down process during the extraction of the samples. This was validated by the abbreviated validation. The following assay was supported by GSK.

	Full Validation	Abbreviated Validation
Studies supported	LAM10014	LAM10017, LAM102611, LEP103944, LAM100034, SCA104648
Analyte	Lamotrigine (GI267119)	Lamotrigine (GI267119)
Matrix	Human Serum	Human Serum
Method	LC/MS/MS	LC/MS/MS
LLOQ	4 ng/mL	4 ng/mL
Linear range	4 to 4000 ng/mL	4 to 4000 ng/mL
QC samples	4.00, 15.0, 350, 3500, 4000 ng/mL	4.00, 15.0, 350, 3500, 4000 ng/mL
Inter-day precision (from QCs)	%CV ≤ 2.6%	N/AP
Accuracy and intra-day precision (from QCs)	0.1% ≤ %bias ≤ 9.7% %CV ≤ 11.3%	0.9% ≤ %bias ≤ 6.2% %CV ≤ 5.7%
Freeze-thaw stability	At least 3 cycles at -30°C	
Bench top Stability at RT	At least 24 hours at room temperature	
Long term at -30° C	At least 220 days	
Stock Solution Stability	At least 195 days at 4°C	
Recovery Low Med High	Not determined. Absolute recovery determination is not a GSK validation requirement. Generic protein precipitation extraction using [redacted] (b) (4) is believed to ensure high recovery and good reproducibility. In addition, the method was sufficiently sensitive at the LLOQ with consistent accuracy and precision over the validated calibration range.	

For initial Clinical Pharmacology studies, the assay validation was supported by [redacted] (b) (4). The model parameters are given in the following Table:

Studies Supported at (b) (4) (b) (4)	LAM10004, LAM10005
Analyte	Lamotrigine (GI267119)
Matrix	Human Serum
Method	LC-MS/MS
LLOQ	4 ng/mL
Linear Range	4 to 4,000 ng/mL
Stock Solution Stability	At least 361 days at 4°C
QC Samples	4, 12, 1600, 3200 & 4000 ng/mL
Inter-day precision (from QC's)	% CV ≤ 2.6
Accuracy & intra-day precision (from QC's)	0.3 % ≤ % Bias ≤ 8.3 % % CV ≤6.3 %
Freeze-Thaw Stability	(b) (4)
Bench Top Stability at Room Temperature	
Long-Term Stability at -20°C	
Recovery Lamotrigine - Low (4 ng/mL) - Medium (2000 ng/mL) - High (4000 ng/mL) (b) (4) Internal Standard	(b) (4)

In general, the assay was adequately validated.

APPENDIX II

OCPB FILING REVIEW

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**N22-115**	**Brand Name**	**Lamictal XR**
OCP Division (I, II, III)	**DCP-I**	**Generic Name**	**Lamotrigine**
Medical Division	**HFD-120**	**Drug Class**	**Phenyltriazine anticonvulsant**
OCP Reviewer	**Veneeta Tandon**	**Indication(s)**	**Adjunctive therapy in partial seizures age 13 an older**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**Extended release tablets, 25, 50, 100 and 200 mg**
		Dosing Regimen	**Once daily with or without food**
Date of Submission	**11/22/06**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**8/15/07**	**Sponsor**	**GSK**
PDUFA Due Date	**9/22/07**	**Priority Classification**	**Standard**
Division Due Date	**8/21/07**		

Clin. Pharm. and Biopharm. Information

Summary: Lamotrigine is currently approved for:

- adjunctive treatment:
  - of partial seizures
  -generalized seizures of Lennox Gastaut syndrome in pediatric and adult patients
  - primary generalized tonic-clonic seizures in adult and pediatric patients, and for
- monotherapy in adults with partial seizures receiving therapy with a single enzyme-inducing AED.
- for maintenance treatment of Bipolar I Disorder to delay time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy.

Dosage forms available are LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets.

The application for LAMICTAL XR Extended-Release Tablets consists of two completed clinical studies in subjects with epilepsy: LAM100034 (adjunctive treatment of partial seizures in subjects >13 years of age), and LEP103944 (open-label study evaluating the conversion from immediate-release to extended-release lamotrigine).

The pharmacokinetics of lamotrigine XR were evaluated in four studies in healthy volunteers; LAM10005 which selected the XR formulations from a number of prototype modified release formulations, LAM10014 evaluated the effect of food on LAMICTAL XR 200mg, LAM10017 explored the relative bioavailability at steady-state of LAMICTAL XR versus IR and dose proportionality, and LAM102611 investigated the effects of esomeprazole on the pharmacokinetics of LAMICTAL XR.

Study LEP103944 evaluated the relative bioavailability of LAMICTAL XR versus IR in subjects with epilepsy.

GSK is currently conducting a study (SCA104648; filed under IND 43,551) evaluating the effects of lamotrigine on QT/QTc interval. Although this study utilizes the immediate-release formulation, GSK considers this supportive information for the extended-release formulation as well. As agreed at the May 25, 2006 pre-NDA meeting, a full report from this study will be provided with the 120-day safety update.

Note: 1. The sponsor has provided the summary upon OCP request based on our QBR.
2. Labeling is provided in the new format (physicians labeling rule)

	"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	7	1	This is considered as 1, although there were 7 different reports
I. Clinical Pharmacology				
Mass balance:	-	-		
Isozyme characterization:	-	-		
Blood/plasma ratio:	-	-		
Plasma protein binding:	-	-		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4	5	
multiple dose:	X	1	1	
Patients-				
single dose:	-			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	-			
fasting / non-fasting multiple dose:	X	1	1	Using all tablet strengths
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			Esomeprazole study
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
Renal impairment:	-			
Hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			Study LAM 100034
Data sparse:	X			Study LEP 103944
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -				
solution as reference:	X			
alternate formulation as reference:	**X**	2	2	3 prototype formulations of ER compared to reference IR
Bioequivalence studies -				
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:	x	2	2	Food effect: With a 200 mg tablet pH effect: Esomeprazole study
Dissolution:	X	1	**1**	
(IVIVC):	**X**	1	1	
Bio-waiver request based on BCS	**-**			
BCS class	**-**			
III. Other CPB Studies	**-**			
Genotype/phenotype studies:	**-**			

Chronopharmacokinetics	**-**			
Pediatric development plan	**-**			
Literature References	-			
Total Number of Studies	**6 PK + 1 conversion study 7 assay reports + 1 PK-PD + 1 IVIVC + 1 dissolution**	**8 PK + 1 PK-PD + 1 IVIVC + 1 dissolution + 1 ethanol effect 1 assay report**		One study submitted with 120 day safety update

Filability and QBR comments

I.	**"X" if yes**	***Comments***
II. Application filable?	***X***	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
III. Comments sent to firm? IV.	**X**	1. The NONMEM control streams and output files should be submitted as text files (*.txt) for the population PK-PD and IVIVC reports.
QBR questions (key issues to be considered)	• What is the relative bioavailability of the ER versus the IR? How can they be switched? • Is there dose proportionality of the ER formulation? • Is there a food effect with the ER formulation? • Is an alcohol induced dose dumping expected with the ER formulation?	
Other comments or information not included above		
Primary reviewer Signature and Date	Veneeta Tandon	
Secondary reviewer Signature and Date	Ramana Uppoor	

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
9/6/2007 06:32:48 AM
BIOPHARMACEUTICS

Jogarao Gobburu
9/6/2007 09:35:41 AM
BIOPHARMACEUTICS

Yaning Wang
9/6/2007 09:47:09 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
9/6/2007 10:15:10 AM
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