Clinical Pharmacology Review

NDA:	20241 (S032) 20764 (S025)
Brand Name:	Lamictal
Generic Name:	Lamotrigine
Type of Dosage Form:	Chewable Dispersible Tablets
Strengths:	2 mg, 5 mg, 25 mg
Indications:	Epilepsy
Type of Submission:	Pediatric Exclusivity sNDA
Sponsor:	GlaxoSmithKline
Submission Date:	11/29/06 1/25/07 2/12/07 2/14/07 3/19/07 3/29/07 4/17/07
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCP Team Leader:	Ramana Uppoor, PhD
Pharmacometrics Reviewer:	Rajnikanth Madabushi, PhD
Pharmacometrics Team Leader:	Yaning Wang, PhD

Table of Contents

1Executive Summary

1.1 Recommendations

We have reviewed the pharmacokinetic data from Studies LAM20006 and LAM20007 and the population PK analysis that evaluated the efficacy and safety of LAMICTAL in pediatric patients (1-24 months of age) with partial seizures. These studies were conducted to fulfill a Pediatric Written Request (WR).

Recommendation

No attempts were made to explore the relationship between the exposure and the pharmacodynamic response. Such an analysis would have provided more insights regarding the effectiveness of Lamictal in the present population (1 month – 24 months), especially given the fact that the primary analysis did not reach pre-specified statistical significance.

Please send the following recommendation to the Sponsor regarding further exposure-response analysis:

Recommendations to the Sponsor:

- Perform an integrated population PK analysis and summarize clearance (L/hr) across all pediatric age groups and adults (for each group of concomitant

antiepileptic drugs (inducers, neutral, and valproic acid)). Only a single integrated analysis will be able to indicate whether clearance is lower in the 2-24 month old population compared to 10 months – 5.3 y.o.

- Explore dose/concentration-percent change in seizure frequency for all the patients in the open label phase using mixed modeling approach.
- Explore dose/concentration-percent change in seizure frequency for the 38 patients who entered the double blind phase. This analysis can utilize both the open label as well as the double blinded phase using mixed modeling approach.
- Compare the exposure-response relationship for neutrals vs valproic acid vs EIAED concomitant treatment groups.
- Further, compare the exposure-response relationship with that observed in older children and adults.
- Please provide the data for exposure – response analysis in the format described in Appendix 1 of the pharmacometrics review (p. 120-123 of this review).

1.2 Phase 4 Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

This supplement to NDA 20241 (S032) and 20764 (S025) was submitted to provide final study reports in fulfillment of the Pediatric Written Request originally issued on December 17, 1998 and modified on July 3, 2000 to study lamotrigine as adjunctive treatment of partial seizures in patients age 1 month to 2 years of age. The submission date for exclusivity was extended to December 1, 2006.

The following studies were stipulated by the Written Request (WR) for lamotrigine:

- Study 1: An open-label lead-in phase, followed by a double-blind, placebo-controlled, randomized, add-on phase assessing the efficacy, safety, and pharmacokinetics of LAMICTAL in pediatric patients (1-24 months of age) with partial seizures. "Standard" PK parameters were to be determined.
- Study 2: An open, uncontrolled, long-term safety study of lamotrigine as add-on therapy in pediatric patients 1 month to 2 years of age with partial seizures.

Studies 1 and 2 in the WR were addressed by Studies LAM 20006 and LAM 20007, respectively. The key findings with respect to the conduct of the PK study and the Clinical Pharmacology of lamotrigine in the pediatric population age 1 month to 2 years of age are as follows:

- Subjects were reasonably distributed across age groups of $\geq$ 6- $\leq$ 12 months or > 12 months old. In study 1 there was only 1 child < 6 months old, and in Study 2 there were 16 subjects < 6 months old. The youngest child in the PK population was 2.4 months old.

- The lamotrigine doses used in the study were titrated up to a maintenance dose. The dosing regimens were on a mg/kg basis. Subjects taking concomitant valproic acid (VPA) or non-enzyme inducing antiepileptic drugs (non-EIAEDs or "neutrals") received the same dose and subjects taking concomitant EIAEDs received a higher dose.
- Clearance was greater in the neutrals and subjects taking EIAEDs than in patients taking VPA. Population PK analysis showed clearance in neutrals was intermediate between Clearance in patients taking EIAEDs and VPA. (b) (4)

(b) (4)

- (b) (4)
- (b) (4)
.

Recommendations

Please refer to Executive Summary, Section 1.1.

Clinical Pharmacology Required Office Level Briefing:
May 16, 2007
Attendees: Atul Bhattaram, John Feeney, Shiew Mei Huang, Kun Jin, Len Kapcala, John Lazor, Larry Lesko, Rajnikanth Madabushi, Mehul Mehta, Atik Rahman, Chandra Sahajwalla, Christoffer Tornoe, Yaning Wang, Ramana Uppoor, Sharon Yan, Sally Yasuda

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neurology Drug Products, DCP I
Office of Clinical Pharmacology

Rajnikanth Madabushi, PhD
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Concurrence: Yaning Wang, PhD
Pharmacometrics Team Leader
Office of Clinical Pharmacology

Ramana Uppoor, PhD
Team Leader, Neurology Drug Products, DCP I
Office of Clinical Pharmacology

cc: HFD-120 NDA 20241 (S032); 20764 (S025)
CSO/J. Reese
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DCP1/M. Mehta

2 Question-Based Review

2.1 General Attributes

What are the general attributes?

Lamotrigine is an anticonvulsant drug. The mechanism of action is unknown. According to the approved labeling, it is rapidly and completely absorbed after oral administration with negligible first pass metabolism, and absolute bioavailability of 98%. The bioavailability is not affected by food. It is metabolized primarily by glucuronic acid conjugation and the major metabolite is an inactive glucuronide conjugate. Following administration of ^{14}C-lamotrigine, 94% was recovered in urine and 2% was recovered in feces.

In patients with epilepsy maintained on other AEDs, there was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50-350 mg twice daily.

The apparent oral clearance of lamotrigine is increased by enzyme inducers including carbamazepine, phenytoin, phenobarbital and primidone. Valproate decreases the apparent clearance of lamotrigine, whether given with or without enzyme inducers.

(b) (4)


(b) (4)

2.2 General Clinical Pharmacology

What are the design features of the clinical studies [redacted] (b) (4) ***?***

[redacted] (b) (4)

- LTG added to VPA or non-EIAEDs

  Week 1 and 2: 0.15mg/kg/day

  Week 3 and 4: 0.3mg/kg/day

  Maximum maintenance dose: 5.1 mg/kg/day or 200 mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 0.3 mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

- LTG added to EIAEDs (maximum of two)

  Week 1 and 2: 0.6mg/kg/day

  Week 3 and 4: 1.2mg/kg/day

  Maximum maintenance dose: 15.6mg/kg/day or 400mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 1.2mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

Once the maintenance dose was reached, subjects in the efficacy study LAM20006 who had a ≥ 40% reduction from baseline seizure frequency during the last 28 days of that optimization period were randomized (1:1) to continued lamotrigine treatment or to a gradual, blinding withdrawal to placebo during the double blind phase (DBP) and remained in the DBP until one of the escape criteria was met.

The subjects in the safety study (LAM20007) were to have remained on an optimized dose of lamotrigine for at least 48 weeks, to assess safety and tolerability and to assess effect of 48 weeks of lamotrigine on seizure frequency.

What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

Study LAM20006 was the pivotal efficacy study. The primary efficacy endpoint was the proportion of subjects receiving lamotrigine vs placebo meeting pre-defined escape criteria (e.g. increase in seizure frequency, onset of new or more severe seizure type, the need to use therapeutic intervention to control seizures, or status epilepticus) during the

double-blind period of the study. Additional data that were collected included reduction in baseline seizure frequency at pre-specified time points during Study LAM 20006 as well as the safety study LAM 20007.

Adverse events noted in the approved labeling include life-threatening serious rash including Stevens Johnson syndrome. There is a boxed warning for serious skin rash. The most common adverse events in adult epilepsy studies were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional common adverse events in children included infection, vomiting, fever, abdominal pain, and tremor, according to the approved labeling.

What are the pharmacokinetic characteristics of lamotrigine in children ages 1 month to 24 months (b) (4)

PK data were collected from a subgroup of subjects in Study LAM 20006. The PK results are shown in the tables below, as provided by the Sponsor. The results are shown by concomitant AED.

Traditional PK data from Week 5 in Study LAM20006 are shown in the table below.

Week 5 PK Data in LAM20006 in Subjects with 8 hour dosing interval

	Enzyme Inducers (n=23) (Dose range 2-17 mg)	**Valproic Acid** (n=8) (Dose Range 2-5 mg)	**Neutral** (n=2) (Dose Range 2 mg only)
Tmax (hrs)	2.0 (0-8)	1.83 (0-6)	4.0 (2-6)
Cmax (µg/ml)	1.25 (42)	2.21 (61)	0.26 (73)
AUC0-8 (µg*hr/ml)	7.38 (37)	16.88 (66)	1.775 (70)
Clss/F (l/hr)	1.34 (37)	0.24 (47)	1.50 (70)
Clss/F (ml/min/kg)	2.44 (41) (range: 1.08-5.21)	0.35 (49) (range: 0.155-0.613)	2.82 (76) (range: 1.26-4.39)
% Degree of fluctuation, mean	66 (n=21)	8	38%
% Swing, mean	105 (n=21)	8	48 %
Weight (kg)	9.3 (20%)	11.8 (14%)	9.3 (11%)

- Generally similar results were observed in traditional PK evaluated in Study LAM 20007. In both cases, there were very few subjects in the groups taking concomitant "neutral" AEDs (or concomitant Valproic Acid" in the case of LAM 20007). However, the results suggest that subjects taking concomitant "neutral" AEDs or enzyme inducing AEDs (EIAEDs) have faster clearance than the subjects taking valproic acid. (b) (4)

(b) (4)

In addition, population PK analysis was performed by the Sponsor and reviewed by Rajnikanth Madabushi. Population PK analysis was conducted using lamotrigine concentrations from LAM20006 and LAM20007. The post-natal age range was 2.4-25.7 months at Week 2 and a corresponding weight range of 3-16.8 kg. The most significant factors affecting apparent oral clearance were concomitant anti-epileptic drug therapy and body weight. Based on Dr. Madabushi's review, the population mean estimate of clearance of lamotrigine in pediatric patients 2 to 26 months of age, weighing 3 to 16 kg was 1.27 to 2.16 mL/min/kg in patients taking carbamazepine, phenytoin, phenobarbital, or primidone; 0.21 to 0.36 mL/min/kg in patients taking valproate; 0.70 to 2.07 mL/min/kg in patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate. The inter-individual variability for the apparent oral clearance was approximately 45%.

Comparison of oral clearance of lamotrigine across different concomitant AED groups after accounting for body weight effects. (from Dr. Madabushi's evaluation).

Concomitant AED	Oral Clearance (L/h)			
	Mean	Median	Min	Max
Inducer	1.03	0.98	0.23	2.68
Neutral	0.66	0.62	0.20	1.49
VPA	0.23	0.19	0.11	0.51

What studies were stipulated by the Written Request and how have these requirements been met from the OCP perspective?

The following studies were stipulated by the Written Request (WR) for lamotrigine:

- Study 1: An open-label lead-in phase, followed by a double-blind, placebo-controlled, randomized, add-on phase assessing the efficacy, safety, and pharmacokinetics of LAMICTAL in pediatric patients (1-24 months of age) with partial seizures. "Standard" PK parameters were to be determined.
- Study 2: An open, uncontrolled, long-term safety study of lamotrigine as add-on therapy in pediatric patients 1 month to 2 years of age with partial seizures.

Study 1 was LAM20006, described above, that enrolled patients aged 1-24 months (in the OLP the youngest was 1 month, and there was only 1 child < 6 months old). Study 2 was LAM20007. The youngest subject in that study was 2 months old, and there were 16 subjects < 6 months old. The majority of subjects in either study were ≥ 6- ≤ 12 months or > 12 months old.

The PK population for Study 1 included 1 child < 6 months old, 27 between 6 months and 12 months old, and 45 greater than 12 months old. The youngest was 4.7 months old. In Study 2 there were 12 subjects in the < 6 months old group who had some PK including 2 with full PK profile; based on population PK data, youngest was 2.4 months at time of PK).

From the OCP perspective, the requirements of the WR have been met.

What was the rationale for selection of dose in the clinical studies [redacted] ?

[redacted]

The [redacted] dose that was studied was 0.15 mg/kg/day at weeks 1 and 2, 0.3 mg/kg/day

at weeks 3 and 4, and increased from week 5 onward to a maintenance dose of 1-5 mg/kg/day. The Sponsor justifies this doubling of the dose in "neutrals" as follows:

The titration and maintenance dosing regimens for LAMICTAL were the same on a mg/kg basis as those recommended for pediatric subjects aged 2-12 years old at the time the studies were initiated (May 2000). At the time, there was no information on initial dosing for the "neutral" treatment group (Patients receiving AEDs other than VPA or EIAEDs) and therefore the dosing guidelines for patients receiving VPA were also utilized for the neutral group.

Subsequent to initiation of LAM20006 and LAM20007, GSK conducted a clinical trial evaluating adjunctive treatment of LAMICTAL for primary generalized tonic-clonic seizures in subjects 2 years of age and older. The titration dosing recommendations specifically for the neutral group were based on population PK analysis with data showing that clearance of lamotrigine in this group was intermediate between that of patients receiving EIAEDs and those receiving VPA. This regimen was approved in September 2006.

(b) (4)

(b) (4)

[redacted]

What were the major findings with respect to efficacy in the pediatric target population?

The primary efficacy endpoint was the proportion of LAMICTAL vs placebo subjects meeting the escape criteria (i.e. treatment failure) during the DBP of the study. In the ITT population the treatment failures in placebo were 84% and in LAMICTAL were 58% ($p = 0.074$). If one of the subjects in the LAMOTRIGINE who discontinued prematurely (but who did not meet escape criteria) is reclassified as a non-treatment failure then the difference in treatment failure rates is statistically significant (84% placebo vs 53% LAMOTRIGINE vs, $p = 0.036$), according to the Sponsor.

Was the formulation used adequate for the age of the population?

Yes. The formulation was a chewable dispersible tablet. The approved Lamictal labeling states that these tablets may be swallowed whole, chewed, or dispersed in water or fruit juice. The labeling also states that food does not affect bioavailability. According to the study report, whole tablets were dispersed in a liquid such as milk, water, or diluted fruit juice and consumed in one dose. (Note, the label does not make recommendations specifically with regard to milk).

Of note, in study LAM20007, a 100 mg chewable dispersible tablet was available in addition to the lower strengths. There is not a marketed 100 mg chewable dispersible tablet.

(b) (4)

[redacted]

Did the analytical method support the pharmacokinetic data?

The bioanalytical methods include serum and saliva measurements of lamotrigine and serum determination of the metabolite GW313090. Reviews of the saliva lamotrigine and serum metabolite assays can be found in the Appendix of this QBR. Only the serum lamotrigine assay will be discussed here since it is relevant to the PK determinations. This was an LC/MS/MS method with an LOQ of 4.0 ng/ml. The reported concentrations were above the LOQ and dilution integrity was demonstrated.

Sample stability is shown below for lamotrigine in serum:

Method	**Freeze-thaw**	**In process**	**Autosampler**	**Long-term stability**
(b) (4) (LC/MS/MS)	3 cycles	24 hours at room temperature; 3 days at 37° C	237 hours (based on reinjection reproducibility)	975 days at -20° C

The assay was adequately documented and validated, although the Sponsor used reinjection reproducibility to support stability of processed samples, and this assumes that the samples were stable prior to the first injection. Duplicate calibration standards and triplicate QC samples were run with each batch of study samples analyzed. Accuracy and precision were within acceptable limits in the validation and in the assay performance.

3 (b) (4)

(b) (4)

4 Appendices

(b) (4)

41 Page(s) has been Withheld in Full as B4 (CCI/ TS) immediately following this page

4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

4.2.1 BIOANALYTICAL METHOD FOR LAMOTRIGINE IN HUMAN SERUM

Serum concentrations of lamotrigine were analyzed using the following method. Lamotrigine and internal standard, [$^{13}C2^{15}N5$]-lamotrigine, were isolated from 0.2 ml aliquots of human serum using solid-phase extraction. The samples were then reconstituted in 50:50 methanol:water and quantified by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the positive ion mode. The method was developed and validated (b) (4)

Standard Operating Procedures were in place for sample preparation, the analytical procedure, and for acceptance of the bioanalytical run (acceptance of calibration standards and quality control (QC) samples).

Selectivity, Accuracy, Precision, and Recovery

Selectivity was addressed using 6 different lots of blank serum or serum containing internal standard and were assayed with all experiments. No chromatographic interferences were observed. A matrix effect of < -6.5% was observed using samples from QC1, QC2, and QC3.

Recovery was approximately 90.46% for lamotrigine and 88.42% for the internal standard.

Ranges of the calibrations curves, LOQ, and nominal values for the QC samples are shown in Table 1 below for the initial validation.

Table 1. Summary of standard curves and QC samples for lamotrigine method validation

Analyte	**Range of Calibration Curve**	**LOQ**	**QC Samples**
Lamotrigine	4 ng/ml 10 ng/ml 40 ng/ml 100 ng/ml 400 ng/ml 1000 ng/ml 2500 ng/ml 3500 ng/ml 4000 ng/ml	4.0 ng/ml	4 ng/ml 12 ng/ml 1600 ng/ml 3200 ng/ml 4000 ng/ml

Linearity of the standard curve was defined and was determined using a weighted ($1/x^2$) linear regression. Duplicate samples were run for the standard curve. Coefficients of determination, r^2, were > 0.9957 in 3 separate validation runs. QC samples were assayed in replicates of 6. The precision for each of the 9 nonzero calibration standards was ≤ 9.58%, and the accuracy ranged from -4.17 to 2.47%. This is acceptable.

Intra-day precision and accuracy for 6 replicates of each of the QC concentrations ranged from 00.26-6.34% and from 0.34-8.27%, respectively. Inter-assay precision and accuracy ranged from 2.05-2.55% and from 2.58-5.21%, respectively. These values are acceptable.

Partial Validation was performed for a 0.05 ml sample aliquot of human serum by evaluating accuracy for calibration data from the one partial validation run and accuracy and precision of QC samples assayed in replicates of 6. The r^2 for the calibration curve was 0.9985 and intra-assay accuracy ranged from -3.14 to 3.57% for the calibration standards. For the QC samples, the intra-assay accuracy ranged from -0.64-8.58% and precision ranged from 0.33-8.47%.

Partial Validation was performed for a 0.05 ml sample aliquot of human plasma. In a single run, the r^2 for the calibration curve was 0.993, and the intra-assay accuracy ranged from -2.59 to 3.08%. For the QC samples the intra-assay accuracy ranged from -4.87 to 4.12% and the precision ranged from 0.44 to 6.73%.

Stability

Stability of lamotrigine was demonstrated as follows using the 12 ng/ml and 4000 ng/ml QC concentrations. Freeze-thaw stability (-20° C) in serum was demonstrated after 3 freeze/thaw cycles**.** In-process stability (serum at room temperature) was demonstrated for 24 hours at room temperature and for 3 days at 37 °C. Stability of processed samples: The Sponsor has used reinjection reproducibility to support the stability of processed samples and this was shown for 237 hours. This assumes that the samples were stable prior to the first injection. This assumption is reasonable since the accuracy (% bias) for each standard was < 10%. Long term stability of lamotrigine in human serum at -20° C was demonstrated for 975 days.

Dilution integrity was demonstrated using a 1:10 dilution of a 12000 ng/ml sample.

Reinjection reproducibility was demonstrated using the range of QC samples after storage at ambient temperature for 237 hours.

The drug solutions for lamotrigine were stable for 28 days at 4° C.

In conclusion, the bioanalytical method used for analysis of lamotrigine in human serum samples in the clinical study in NDA 20241 (S-032) is adequately documented and validated.

4.2.2 BIOANALYTICAL METHOD FOR LAMOTRIGINE IN HUMAN SALIVA

Saliva concentrations of lamotrigine were analyzed using the following method. Lamotrigine and internal standard, [$^{13}C_2{}^{15}N_5$] – lamotrigine were isolated from 50 µL aliquots of human saliva using solid-phase extraction. The samples were then reconstituted in 50:50 methanol:water and quantified by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the positive ion mode. The method was developed and validated (b) (4)

Standard Operating Procedures were in place for sample preparation, the analytical procedure, and for acceptance of the bioanalytical run (acceptance of calibration standards and quality control (QC) samples).

Selectivity, Accuracy, Precision, and Recovery

Selectivity was addressed using 3 lots of blank human saliva. No chromatographic interferences were observed. A matrix effect was observed of -8.23% lamotrigine (suppression was -13.95% at the LLQ QC, -10.45% at QC2 and -0.3% at the ULQ QC).

Recovery from saliva was approximately 92.96% for lamotrigine and 90.34% for the internal standard.

Ranges of the calibrations curves, LOQ, and nominal values for the QC samples are shown in Table 1 below for the initial validation.

Table 1. Summary of standard curves and QC samples for saliva lamotrigine method validation

Analyte	**Range of Calibration Curve**	**LOQ**	**QC Samples**
Lamotrigine	4 ng/ml 10 ng/ml 40 ng/ml 100 ng/ml 400 ng/ml 1000 ng/ml 2500 ng/ml 3500 ng/ml 4000 ng/ml	4.0 ng/ml	4 ng/ml (LLQ QC) 12 ng/ml (QC1) 1600 ng/ml (QC2) 3200 ng/ml (QC3) 4000 ng/ml (ULQ QC)

Linearity of the standard curve was defined and was determined using a weighted ($1/x^2$) linear regression. Duplicate samples were run for the standard curve. Coefficients of determination, r^2, were > 0.992 in 3 separate validation runs. The precision and accuracy for each of the 9 nonzero calibration standards ranged from 1.10-6.32% and from -9.32-10.41%, respectively. This is acceptable.

Intra-day precision and accuracy for 6 replicates of each of the QC concentrations ranged from 0.72-8.65% and from -1.61- 12.08%, respectively. Inter-assay precision and accuracy ranged from 0.79 to 2.35% and from -0.15 to 11.2%, respectively. These values are acceptable.

Stability

Stability of lamotrigine in saliva was demonstrated as follows. Freeze-thaw stability (-20° C) in saliva was demonstrated after 3 freeze/thaw cycles using QC1 and ULQ QC samples. In-process stability (saliva at room temperature) was demonstrated for 24 hours using the QC1 and the ULQ QC samples. Stability of processed samples: The Sponsor has used reinjection reproducibility to support the stability of processed samples and this was shown for 46 hours. This assumes that the samples were stable prior to the first injection. This assumption is reasonable since the accuracy (% bias) for each standard was < 11%. Long term stability at -20° C was demonstrated for 222 days using QC1 and ULQ QC samples.

Dilution integrity of lamotrigine was demonstrated using a 10-fold dilution of a 12000 ng/ml concentration.

Reinjection reproducibility was demonstrated after 46 hours at ambient temperature using QC3 and ULQ QC samples.

Stability of stock solutions was shown after storage for 28 days at 4 ° C during the validation for lamotrigine in serum.

In conclusion, the bioanalytical method used for analysis of lamotrigine in saliva samples in the clinical studies in NDA 20241 (S032) is adequately documented and validated.

4.2.3 BIOANALYTICAL METHOD FOR METABOLITE GW313090 IN SERUM

GW313090 is a cardioactive metabolite previously identified in dogs but not in humans. Serum concentrations of GW313090 (lamotrigine metabolite) were analyzed using the following method. GW313090 and internal standard, [$^{13}C_2{}^{15}N_5$] - GW313090 were isolated from 50 µL aliquots of human serum using solid-phase extraction. The samples were then reconstituted 50:50 methanol:water and quantified by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the positive ion mode. The method was developed and validated (b) (4)

Standard Operating Procedures were in place for sample preparation, the analytical procedure, and for acceptance of the bioanalytical run (acceptance of calibration standards and quality control (QC) samples).

Selectivity, Accuracy, Precision, and Recovery

Selectivity was addressed using 6 different lots of blank human serum. No chromatographic interferences were observed. A matrix effect was observed of -37.67% for GW313090 and -41.58% for internal standard. This indicates suppression of ionization, and it was similar for metabolite and internal standard.

Recovery was approximately 80.03% for GW313090 and 72.27% for the internal standard.

Ranges of the calibrations curves, LOQ, and nominal values for the QC samples are shown in Table 1 below for the initial validation. (Calibration standards and QC samples were prepared containing both lamotrigine and GW313090). The actual assay was performed with standards that included only GW313090. However, since the methods measure specific metabolite ion transition this is not likely to confound the assay.

Table 1. Summary of standard curves and QC samples for serum GW313090 method validation

Analyte	Range of Calibration Curve	LOQ	QC Samples
GW313090	4 ng/ml 12 ng/ml 30 ng/ml 75 ng/ml 150 ng/ml 250 ng/ml 375 ng/ml 500 ng/ml	4.0 ng/ml	4 ng/ml (LLQ QC) 12 ng/ml (QC1) 200 ng/ml (QC2) 400 ng/ml (QC3) 500 ng/ml (ULQ QC)

Linearity of the standard curve was defined and was determined using a weighted (1/x) linear regression. Duplicate samples were run for the standard curve. Coefficients of determination, r^2, were > 0.999 in 3 separate validation runs. The precision for each of the 8 nonzero calibration standards was ≤ 3.82 %, and the accuracy ranged from -1.07 to 1.19%. This is acceptable.

Intra-day precision and accuracy for 6 replicates of each of the QC concentrations ranged from 0.65-6.99% and from -3.77- 10.81%, respectively. Inter-assay precision and accuracy ranged from 0.14 to 2.69% and from -1.90 to 8.13%, respectively. These values are acceptable.

Stability

Stability of GW313090 was demonstrated as follows. Freeze-thaw stability (-20° C) in serum was demonstrated after 3 freeze/thaw cycles using QC1 and ULQ QC samples. In-process stability (serum at room temperature) was demonstrated for 24 hours for QC1 and the ULQ QC samples. Room temperature stability was demonstrated at the end of 7 days in which the LLQ and ULC QC samples had accuracy and precision that were acceptable (compared to the nominal concentrations), and QC samples 1-3 had acceptable precision, with percent deviation from time 0 of ≤16.6%. Stability of processed samples: The Sponsor has used reinjection reproducibility to support the stability of processed samples and this was shown for 66 hours. This assumes that the samples were stable prior to the first injection. This assumption is reasonable since the accuracy (% bias) for each standard was < 10%. Long term stability at -20° C was demonstrated for 117 days using QC1, QC2, and QC3.

Dilution integrity of GW313090 was demonstrated using a 10-fold dilution of a 1500 ng/ml concentration.

Reinjection reproducibility was demonstrated using control samples after storage for up to 66 hours at room temperature for each of the QC samples by reinjecting a set of previously assayed standards and QC samples that had been stored after injection at room temperature.

Stability of stock solutions was shown after storage for 93 days at 4 ° C.

In conclusion, the bioanalytical method used for analysis of GW313090 in serum samples in the clinical studies in NDA 20241 (S032) is adequately documented and validated.

4.2.4 PLACEBO-CONTROLLED EFFICACY STUDY LAM20006

A DOUBLE-BLIND, PLACEBO-CONTROLLED, ADD-ON CLINICAL TRIAL OF THE SAFETY, PHARMACOKINETICS AND EFFICACY OF LAMICTAL IN PEDIATRIC AGE SUBJECTS (1-24 MONTHS)

Study Investigators and Site: Multiple sites

Protocol Number: LAM20006

OBJECTIVE:

The primary objective was to compare efficacy of LAMICTAL add-on therapy to placebo in subjects 1-24 months old with partial seizures. Secondary objectives were to 1) assess safety of LAMICTAL as add-on therapy in subjects 1-24 months old and 2) determine the pharmacokinetics of lamotrigine in these subjects.

FORMULATIONS:

Table 1. Product used in LAM20006

	Batch Number	Date of Manufacture (Dates of study)
LAMICTAL 2 mg chewable tablet	OZM2312, OZM2301	(Exp. Date 8/31/04) (5/19/00-11/25/03)
LAMICTAL 5 mg chewable tablet	WNT542002, B019235	(Exp. Date 2/28/03; 8/31/05) (5/19/00-11/25/03)
LAMICTAL 25 mg chewable tablet	WNT543003, B050869	(Exp. Date 8/31/04; 10/31/06) (5/19/00-11/25/03)
Placebo (matching)	OZM2313, 1ZM0267, WT384005, B019131, WT385008, B015055	(5/19/00-11/25/03)

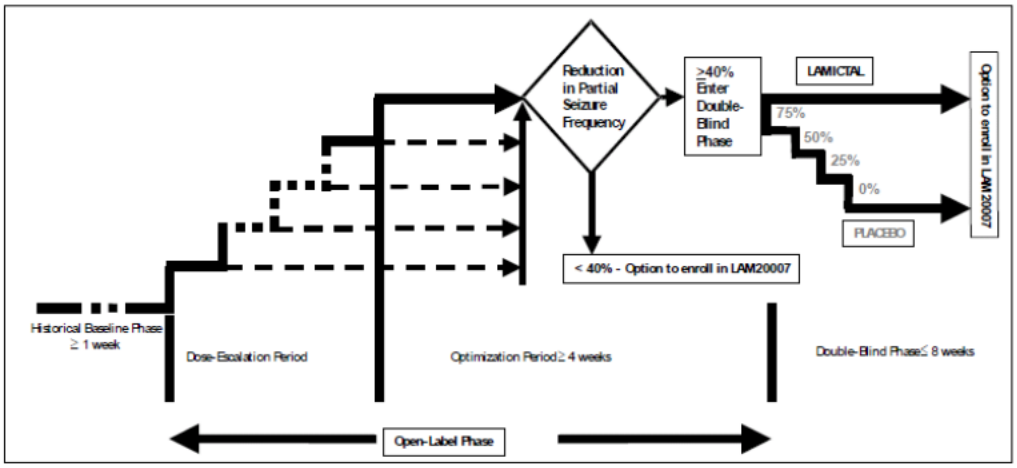
(b) (4)

[redacted]

STUDY DESIGN:

This was an international, multi-center study consisting of an open-label period (OLP) followed by a parallel, randomized, double-blind, placebo controlled period, as shown in the figure below. This was a responder-enriched design that was chosen by the Sponsor to provide evaluation of efficacy in infants while minimizing exposure to placebo.

Figure 1 **Safety, Pharmacokinetics, and Efficacy of Add-on LAMICTAL in Pediatric Age Subjects (1-24 months) with Partial Seizures (LAM20006)**



Eligible subjects received LAMICTAL as an add-on therapy during the OLP. Dosing regimens were based on concomitant AED as described below. The dose of LAMICTAL was titrated by investigators until, in their opinion optimal clinical benefit (maximum seizure control and minimum adverse experiences) had been achieved. The period of optimal clinical benefit, or optimization, had to be maintained for at least 4 weeks (i.e. 28 days) during which there could be no changes to the background AEDs. Additionally, LAMICTAL doses were to remain unchanged during the last 2 weeks of the optimization period. The OLP could be no longer than 23 weeks for subjects receiving enzyme inducing antiepileptic drugs (EIAEDs) or 27 weeks for subjects receiving concurrent valproic acid or non- EIAEDs. Subjects achieving a ≥40% reduction from baseline in partial seizure frequency during the last 28 days of the optimization period were randomized (1:1) to either continued LTG treatment or a gradual, blinded withdrawal of LTG to placebo (reduction by 25% every week). Subjects remained in the Double-Blind Phase (DBP) for 8 weeks or until one of the escape criteria was met. The primary efficacy endpoint was the proportion of subjects receiving lamotrigine vs placebo meeting the escape criteria during the DBP of the study. Escape criteria were as follows:

- 50% or greater increase in monthly partial seizure frequency compared to the frequency of seizures during the Optimization Period. Monthly seizure frequency was computed using the last 4 weeks of the optimization period and the most recent 4 weeks of the DBP. If a subject had not reached 4 weeks in the DBP but had already experienced a total number of seizures ≥150% of the seizures of the Optimization Period, the subject was considered to have met the escape criterion;
- Doubling of the highest consecutive 2-day partial seizure count observed during the Optimization Period;
- Onset of a new and more severe seizure type;
- Clinically significant worsening of non-partial seizures observed during the Historical Baseline Phase or the Optimization Period;
- The need to use any therapeutic intervention to control seizures; or
- Status epilepticus.

PK measurements

At the end of Week 2 in the OLP, a blood sample was collected to determine LTG serum concentration and adjustments to dose escalation, if necessary. This sample was collected as close to the middle of the dosing interval as possible. If the lamotrigine concentration in this sample was higher than 0.41 µg/ml, the concentration found in adults at Week 2, subsequent doses for this subject during the dose escalation phase were reduced by a pre-specified percentage based on weight. For subjects needing a dose adjustment to their Week 2 LTG concentrations, an additional blood sample was to be collected 2 weeks later to re-evaluate serum concentration. Pharmacokinetic samples were collected from consenting subjects at approximately the end of Week 5 (for subjects receiving an EIAED) or at the end of week 6 (for subjects receiving a non-EIAED or valproic acid) of the OLP. These samples were to be collected pre-dose and at 1, 2, 3, 4, 6, and 8 hours after the dose. If it was not possible to obtain all blood samples, saliva samples were to be collected at all the time points and blood samples at only pre-dose, 2, and 6 hours post-dose. In addition, a blood sample was collected at the end of the OLP for determination of lamotrigine (originally collected for determination of the presence of the 583C80 metabolite).

Dosing

Initial dosing of lamotrigine was every other day when necessary. Lamotrigine was given using an every 8 hours dosing schedule once a large enough total daily dose was reached. Whole tablets were dispersed in a liquid such as milk, water, or diluted fruit juice, and consumed in one dose. Pureed or semi-soft food could also be used to disperse the tablets. (***Note:*** the approved labeling states that the dispersible tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice; it does not make recommendations with regard to milk. The label states that food does not affect bioavailability).

During the Dose-Escalation Period, lamotrigine was administered as follows:

- LTG added to VPA or non-EIAEDs

  Week 1 and 2: 0.15mg/kg/day

  Week 3 and 4: 0.3mg/kg/day

  Maximum maintenance dose: 5.1 mg/kg/day or 200 mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 0.3 mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

- LTG added to EIAEDs (maximum of two)

  Week 1 and 2: 0.6mg/kg/day

  Week 3 and 4: 1.2mg/kg/day

  Maximum maintenance dose: 15.6mg/kg/day or 400mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 1.2mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

Dosing intervals were based on weight as shown below:

Dose	Weight	Dosing Interval
0.15 mg/kg/day	7-12 kg	qod
	≥13 kg	qd
0.3 mg/kg/day	7-12 kg	qd
	≥13kg	bid
0.6 mg/kg/day	3 kg	qod
	3.5-6 kg	qd
	6.5-7.5 kg	bid
	≥8 kg	tid

Subjects completing the study or meeting escape criteria during the DBP were considered "completers". Subjects who were not eligible for randomization at the end of the OLP were considered "withdrawn".

Inclusion/Exclusion Criteria

Inclusion criteria included male or female pediatric subjects (age 1-24 months) diagnosed with epilepsy whose partial seizures were uncontrolled by one or more marketed antiepileptic drugs (AEDs). AEDs could include vigabatrin. All subjects must have consistently exhibited at least 4 reliably detectable partials seizures per month to be eligible. Subjects on non-enzyme inducing antiepileptic drugs (Non-EIAEDs), including valproic acid were to weigh at least 6.7 kg at study entry. Exclusion criteria included seizures not related to epilepsy, previous treatment with lamotrigine, maintenance regimen of more than two background AEDs, taking valproic acid with one or more additional AEDs, had taken valproic acid for < 6 months or >6 months and had evidence of hepatic dysfunction, currently taking felbamate or ACTH. Subjects who were on 3 background AEDs were tapered off of one AED while simultaneously beginning the dose escalation phase. Changes to background AEDs (only deletions) could be made during the Dose-Escalation Period as long as the subject remained on one or 2 background AEDs. If the subject was taking Valproic Acid as a background AED, then it was the only background AED that could be used.

ASSAY:

Table 2. Performance of Analytical Methods for Lamotrigine study LAM20006

Analyte	Method	Calibration Standards (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Lamotrigine (Serum)	LC/MS/MS	4-4000 ng/ml	r > 0.995	4.0 ng/ml	12.0	5.3	2.8
					1600.0	2.4	1.3
					3200.0	3.5	0.1
Lamotrigine (Saliva)	LC/MS/MS	4-4000 ng/ml	r > 0.988	4.0 ng/ml	12.0	9.3	0.4
					1600.0	4.2	-0.2
					3200.0	4.9	-0.9
583C80 * (serum)	LC/MS/MS	4-500 ng/ml	r > 0.997	4.0 ng/ml	12.0	4.6	7.0
					200	2.0	0.6
					400	2.5	-2.2

*also referred to as metabolite GW313090

Serum and saliva samples were stored at -20º C until analysis. Each batch of samples was run against duplicate calibration standards (9 nonzero standards for lamotrigine and 8 for GW313090) along with triplicate QC samples. QC samples and calibration standards met acceptable criteria. Samples were analyzed from 6/5/02-2/25/04. The Sponsor states that human serum and saliva lamotrigine PK samples were analyzed on an ongoing basis within their documented periods of frozen storage stability. The reported concentrations were all above the LOQ. The assay is acceptable.

RESULTS:

Demographics

One hundred and seventy-seven subjects were enrolled in the OLP, and 139 of those prematurely discontinued the OLP. The majority that discontinued (80 subjects) failed to meet the criteria for randomization to double-blind treatment. Fourteen subjects withdrew due to adverse events. A total of 38 subjects were randomized to the DBP (19 in the placebo group and 19 in the Lamictal group). Seventeen subjects in the LAMICTAL group and 19 in the placebo group completed the DBP of the study.

The Safety population included any subject who took at least 1 dose of study medication. The primary efficacy analyses were performed on the "Intent to Treat" (ITT) DBP (all randomized subjects who took at least 1 dose of study medication during the DBP) and the "Per Protocol" (PP) DBP population. The demographics of the safety population and by randomization in the ITT DBP population are shown in the table below, as provided by the Sponsor.

Table 9 Demographic Characteristics (Safety Population – LAM20006)

Demographic Characteristic	OLP LAMICTAL (N=177)	ITT – DBP (N=38)	
		Placebo (N=19)	LAMICTAL (N=19)
Gender - n (%)			
Male	92 (52%)	9 (47%)	12 (63%)
Female	85 (48%)	10 (53%)	7 (37%)
Age (months)			
Median	13.17	14.16	13.54
Range	1.0 – 24.0	2.0 - 23.3	6.6 – 23.9
Age group (months)			
<6	28 (16%)	1 (5%)	0
≥6 - ≤12	56 (32%)	6 (32%)	8 (42%)
>12	93 (53%)	12 (63%)	11 (58%)
Race - n (%)			
White	149 (84%)	17 (89%)	17 (89%)
Black	13 (7%)	0	0
American Hispanic	9 (5%)	2 (11%)	1 (5%)
Asian	2 (1%)	0	0
Other	4 (2%)	0	1 (5%)
Weight (kg)			
Median	9.60	10.10	10.00
Range	2.9 – 17.3	4.5 - 13.2	7.1 – 17.3

Source Data: Table 12.4

In the OLP group, 126 subjects were taking EIAEDs (phenobarbital, carbamazepine, phenytoin, primidone, or pentobarbital) and 51 were taking non-EIAEDs (topiramate, clonazepam, vigabatrin, clobazam, oxcarbazepine, zonisamide, lorazepam, nitrazepam, clorazepate, diazepam,

gabapentin, levetiracetam, or adrenocorticotropic hormone) or valproic acid. In the ITT group, EIAEDs were used in 14 placebo /13 LAMICTAL subjects, and non-EIAEDs were taken by 5 placebo/ 6 LAMICTAL subjects.

The PK data for this study included 1 child < 6 months old, 27 between 6 months and 12 months old, and 45 children greater than 12 months old. The youngest child in the PK population was 4.7 months old. (The youngest child in the study was 1 month old in the OLP).

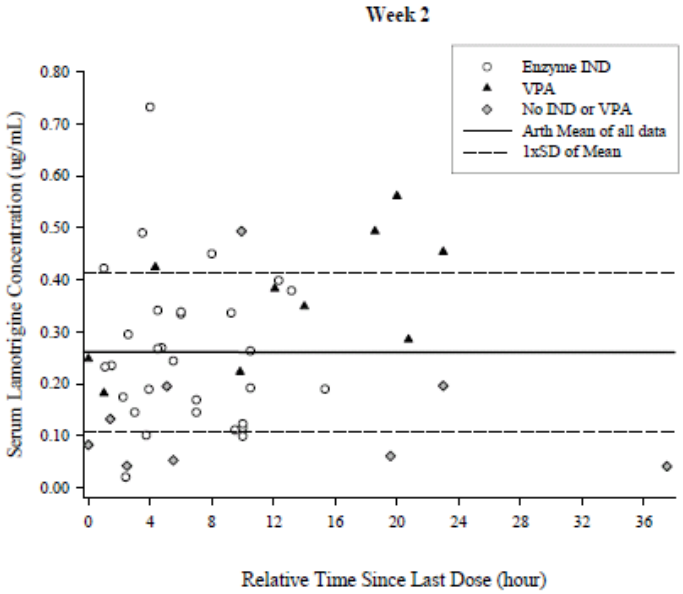
LAMOTRIGINE Pharmacokinetics

A total of 51 subjects at Week 2 provided serum LTG concentrations. These are presented in the table and the figure (as provided by the Sponsor) below, summarized by concomitant medication. (The subjects taking VPA alone or patients taking non-EIAEDs had the same dosage regimen).

	Lamotrigine Concentration (µg/ml) in subjects on **Inducer AEDs**	Lamotrigine Concentration (µg/ml) in subjects on **VPA only (inhibitors)**	Lamotrigine Concentration (µg/ml) in subjects on **Non-Inducers (Neutrals)**
Mean (% CV)	0.259 (56)	0.360 (35)	0.144 (100)
Range	0.02-0.732	0.182-0.561	0.041-0.493
N	31	10	9

(note: these data are corrected based on Sponsor's email of 3/23/07 that reclassified 3 subjects in the PK data set only due to initially incorrect classification of concomitant therapy, although it was correctly classified in the clinical data)

Figure 16.1 Individual Serum Lamotrigine Concentrations At Week 2 and End of Open Label Phase (Updated)



The percentage change in the OLP Partial Seizure Frequency at Study Week 2 for each concomitant AED group is shown in the table below (data provided in Sponsor's email of 3/23/07).

Concomitant AED Group	**N**	**Median Percent Reduction in Seizure Count**
Induced	121	8.6
Neutral	34	25.7
Valproic Acid	15	0

The mean prescribed dose for the induced subjects was 0.6 mg/kg/day, and the mean for the neutral subjects and the VPA subjects was 0.2 and 0.14 mg/kg/day, respectively.

Week 5 PK data

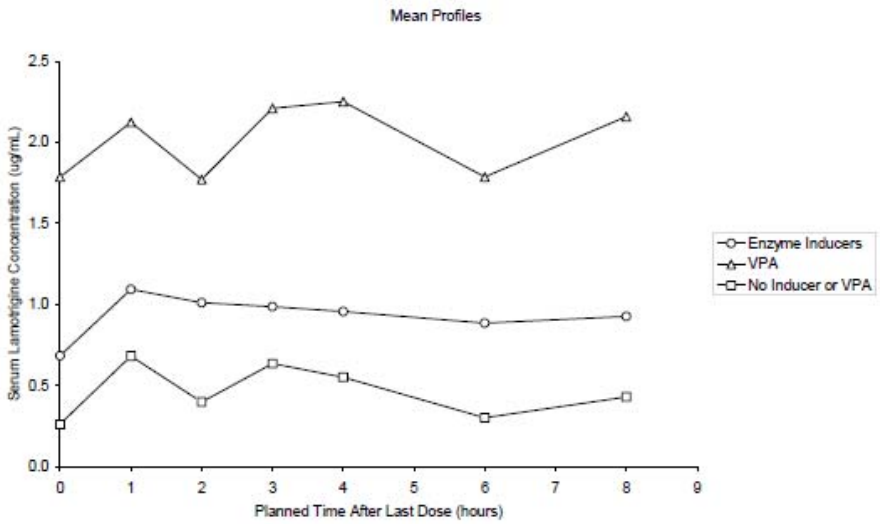
Noncompartmental PK parameters at Week 5 were derived in 35 subjects. Results are shown below by concomitant AED classification for only those subjects who had a dosing interval of every 8 hours (excluding 1 subject on valproic acid and 1 neutral subject) . Data shown are arithmetic mean (%CV) for PK parameters derived by the Sponsor. Tmax* values are median (range). Limitations of this data set include few time points in some cases and few subjects in the neutral group. Values may not reflect steady state in all cases since in some cases the subject received a new dose on the Week 5 PK study day.

Week 5 PK Data in LAM20006 in Subjects with 8 hour dosing interval

	Enzyme Inducers (n=23) (Dose range 2-17 mg)	**Valproic Acid** (n=8) (Dose Range 2-5 mg)	**Neutral** (n=2) (Dose Range 2 mg only)
Tmax (hrs)	2.0 (0-8)	1.83 (0-6)	4.0 (2-6)
Cmax (µg/ml)	1.25 (42)	2.21 (61)	0.26 (73)
AUC0-8 (µg*hr/ml)	7.38 (37)	16.88 (66)	1.775 (70)
Clss/F (l/hr)	1.34 (37)	0.24 (47)	1.50 (70)
Clss/F (ml/min/kg)	2.44 (41) (range: 1.08-5.21)	0.35 (49) (range: 0.155-0.613)	2.82 (76) (range: 1.26-4.39)
% Degree of fluctuation, mean	66 (n=21)	8	38%
% Swing, mean	105 (n=21)	8	48 %
Weight (kg)	9.3 (20%)	11.8 (14%)	9.3 (11%)

These data have been calculated that reflects correct classification by concomitant drug and dosing interval of every 8 hours.

The mean plasma-concentration time course profiles at Week 5 for the subjects who received lamotrigine with an 8 hour dosing interval are shown in the figure below, as provided by the Sponsor (submitted on April 17, 2007).



Despite the limitations of the data set, the data suggest that clearance is greater in the inducer and neutral groups than in the valproic acid group, as previously described in the labeling. Cmax values for subjects taking inducers or neutral drugs were approximately 57% and 12%, respectively of the Cmax values of subjects taking VPA (although it is noted that there were only 2 subjects in the neutral group and there was an approximate 3-fold range in the Cmax values in that group).

Reduction in seizure frequency at Week 5 is shown in the table below, as provided by the Sponsor.

Concomitant AED Group	**N**	**Median Percent Reduction in Seizure Count**	**Mean Actual Prescribed Total Daily Dose (mg/kg/day)**
Induced	118	32.3	2.13
Neutral	32	26.6	0.5
Valproic Acid	15	0	0.49

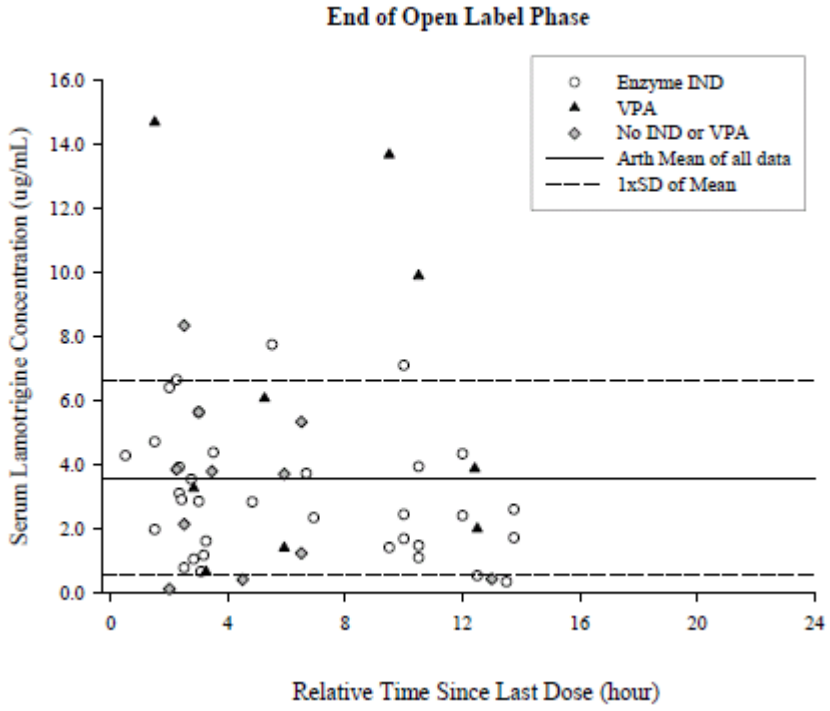
PK at End of Open Label Phase

Plasma concentrations of lamotrigine taken from a single sample at the end of dosing otpimzation (end of the OLP) are shown in the table and figure below. Similar to the results seen at week2 and week 5, concentrations in subjects taking valproic acid are, on average, higher than concentrations in the other 2 groups following dosing optimization. Concentrations in the induced group are similar to those in the neutral group.

Table 24 Summary Serum LTG Concentrations (ug/mL) At End of Open Label Phase

	Enzyme Inducers (N=32)	VPA (N=10)	No Inducer or VPA (N=12)
Dose Range (mg)	2.0–72.0	2.0–19.0	2.0–49.0
Arth Mean	3.10	5.80	3.05
GeoMean	2.41	3.84	1.81
Range	0.348–7.75	0.654–14.7	0.126–8.35

Source: Table 16.4.



Reduction in seizure frequency in the last 28 days of the OLP is shown in the table below, as provided by the Sponsor, along with Total Daily Dose by AED.

Concomitant AED Group	**N**	**Median Percent Reduction in Seizure Count**	**Mean Actual Prescribed Total Daily Dose (mg/kg/day)**
Induced	122	46.7	9.26
Neutral	34	74.3	3.38
Valproic Acid	16	73.9	2.78

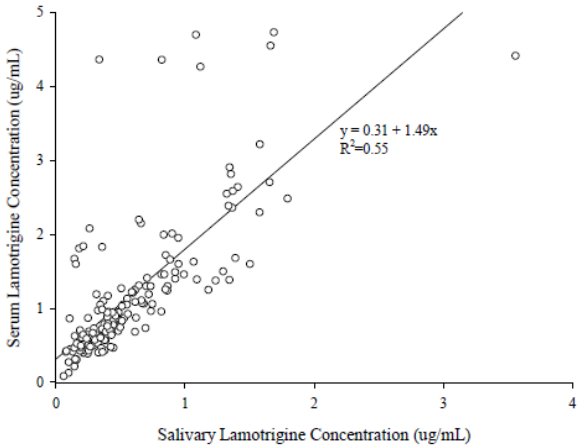
Saliva Lamotrigine PK at Week 5

Saliva LTG concentrations and their ratios to a measured serum LTG concentration determined at the same time point were tabulated. Since it has previously been reported that saliva: serum

concentration ratios for LTG approximate the drug's unbound fraction in plasma (approximately 50% in adults), the Sponsor believed that saliva: serum ratios > 1 would be unlikely and that these high concentrations could be due to drug contamination of a sample due to residual drug in the mouth or from evaporative loss during storage. Therefore, the Sponsor has not used anomalously high values that result in ratios of > 1 (n=40 out of 211 total saliva/serum concentration ratios in 39 subjects).

The mean (range) time deviation between collection of a saliva sample from its respective serum sample was 0.02 hours (-0.33 to 0.25). The mean (range) saliva: serum ratio across all subjects was 0.52 (0.08-0.99) after removal of ratios > 1.0. The correlation between serum and saliva concentrations is shown below, as provided by the Sponsor. This relationship was not dependent on time or serum LTG concentration. The results suggest variability in the ratios, leading to some outliers in the correlation between saliva and serum concentrations.

Figure 16.4 Correlation Between Serum and Saliva Lamotrigine Concentrations



NB: All saliva data associated with a saliva/serum ratio > 1 removed from this correlation.

The Sponsor used salivary non-compartmental PK parameters in 16 subjects to predict serum values using the saliva/serum ratios. Using either individual average ratios or the population average ratio the ratios of predicted serum concentrations to observed concentrations are shown in the table below, as provided by the Sponsor. In neither case dose the saliva ratio accurately predict the serum ratio.

Table 26 Summary (N=16) Ratios of C_{max}, CL_{ss}/F and $C_{predose}$ Predicted From Saliva Relative to That Observed in Serum

	C_{max} (pred)/ C_{max} (serum)	CLss/F (pred)/ CLss/F (serum)[a]	$C_{predose}$ (pred)/ $C_{predose}$ (serum)
Based on Individual Average Saliva/Serum Ratios			
Arth Mean	1.53	0.95	0.96
GeoMean	1.41	0.95	0.94
Range	0.87-4.04	0.66-1.03	0.58-1.48
Based on Population Average Saliva/Serum Ratio (i.e., 0.52)			
Arth Mean	1.28	1.27	0.87
GeoMean	1.18	1.16	0.79
Range	0.56-3.08	0.83-3.71	0.25-1.83

Source: Table 16.11 and Table 16.12
a. N=15. .

Serum 583C80 Concentrations at end of OLP

583C80 was quantifiable in only 1 subject. The concentration was 24.04 ng/ml. The Sponsor states that this subject had no adverse cardiac events.

Pharmacodynamic Analysis: Primary Efficacy Analysis

Efficacy will not be reviewed in detail by OCP. The primary efficacy endpoint was the proportion of LAMICTAL vs placebo subjects meeting the escape criteria (i.e. treatment failure) during the DBP of the study. The results are shown in the table below, as provided by the Sponsor. The difference between treatment groups did not achieve statistical significance. However, two treatment failures in the LAMOTRIGINE group discontinued prematurely without having met escape criteria. One of those subjects met escape criteria with a more than 50% increase in seizure counts while the other subject did not. The latter subject was treated in the DBP for 30 days and had a partial seizure reduction of 57% at the time of discontinuation. If that subject is reclassified as a non-treatment failure, then the difference in treatment failure rates is statistically significant (53% LAMOTRIGINE vs 84% placebo, p = 0.036), according to the Sponsor. This will be reviewed in detail by the Medical Officer.

Table 12 Proportion of subjects who met escape criteria during the DBP (LAM20006)

	Placebo		LAMICTAL		
Analysis Population	N	Treatment Failures	N	Treatment Failures	p-value[1]
ITT DBP[2]	19	16 (84%)	19	11 (58%)	0.074; 0.151
PP DBP	17	14 (82%)	17	9 (53%)	0.067; 0.141

Source data: Table 13.1

1. p-values: two tailed chi-square test and Fisher's exact test, respectively
2. Two LAMICTAL subjects who did not meet escape criteria but discontinued prematurely were counted as treatment failures in the ITT DBP analysis.

Safety

Safety results will not be reviewed in detail by OCP. Briefly, the Sponsor states that the majority of subjects (89%) experienced at least one adverse event (AE) during the OLP. The most common AEs included pyrexia (41%), upper respiratory tract infection (19%), vomiting (19%), nasopharyingitis (16%) and rash (15%). The most common treatment-related AE during the OLP was rash that occurred in 6 (3%) of the subjects.

Twenty-three percent of subjects reported a serious AE (SSAE) during the OLP. The most common were seizures, pneumonia, and cyanosis. One subject reported a case of rash that was considered a SAE but that was considered to be viral. In the DBP, one case of rash was reported for a subject randomized to Lamotrigine that was mild in intensity. The subject remained in the study.

In the DBP, one subject in the placebo group and one in the Lamictal group experienced a SAE (status epilepticus in the placebo treated subject and bronchitis in the LAMICTAL treated subject).

CONCLUSIONS:

The conclusions from a clinical pharmacology perspective are as follows:

- Subjects taking neutral AEDs or EIAEDs had greater lamotrigine clearance than did subjects taking valproic acid.
- Subjects taking neutral drugs or valproate concomitantly with lamotrigine were assigned to receive the same initial mg/kg doses, with mean total daily dose at the end of the OLP only 22% greater in neutrals than in valproic acid subjects.
- Although median reduction in seizure count is not a primary efficacy endpoint, data for this measure available throughout the open label period do not suggest that "neutral" subjects had a lower response in this measure, despite lower plasma concentrations than observed in the subjects with either valproic acid or EIAEDs.

4.2.5 SAFETY STUDY LAM20007

AN OPEN-LABEL, UNCONTROLLED, LONG-TERM STUDY TO ASSESS THE SAFETY OF LAMICTAL IN PEDIATRIC SUBJECTS PREVIOUSLY ENROLLED IN PROTOCOL LAM20006 AND IN LAMICTAL-NAÏVE SUBJECTS (1-24 MONTHS OF AGE)

Study Investigators and Site: International, multi-center

Protocol Number: LAM20007

OBJECTIVE:

The objectives were to assess safety and tolerability of LAMICTAL (LTG) in pediatric subjects with epilepsy; to assess the effect of 48 weeks administration of LTG on seizure frequency to determine the PK of lamotrigine in LTG-naïve pediatric subjects (age 1-24 months) with partial seizures; and to provide 48 weeks of additional treatment for subjects who participated in LAM20006.

FORMULATIONS:

Table 1. Product used in LAM20007

	Batch Number	Exp. Date (Dates of study)
LTG 2 mg chewable tablet	9ZM2276, 9ZM2277, 0ZM0301, 0ZM0302, OZM2312, OZM2301, 2ZM0528, 3ZM3053	Exp. Date 10/31/03; 12/31/03;2/28/04;4/30/04;8/31/04; 2/28/06; 10/31/07 (9/5/00-1/6/06)
LTG 5 mg chewable tablet	3362G/A, WNT542002, B019235, B095144, B138952	Exp. Date 7/31/01; 2/28/03;8/31/05; 2/28/08; 9/30/09 (9/5/00-1/6/06)
LTG 25 mg chewable tablet	3363E/A, WNT543001, WNT543003, B050869, B099333, B138872	Exp. Date 8/31/01; 2/28/03; 8/31/04;10/31/06; 4/30/;08;9/30/09; 9/30/05; (9/5/00-1/6/06)
LTG 100 mg chewable tablet	3372D/A, 3393A, WNT544004, B038383, B096455, B139294	Exp. Date 9/30/01; 10/31/01; 8/31/04; 6/30/06; 3/31/08; 9/30/09; 9/30/05 (9/5/00-1/6/06)

(b) (4)

(b) (4)

STUDY DESIGN:

This was an international, multi-center study using an uncontrolled open-label design. During the Screen Phase, for LTG-naïve subjects this was a historical baseline phase of at least 7 days that also included baseline assessments. For previous LAM20006 subjects, the LAM20006 final visit assessments served as the Screen assessments.

Treatment Phase: For LTG-naïve subjects, regular clinical visits were performed at 2-week intervals during the first 8 weeks of dose escalation. Additional safety assessments for LTG-naive subjects included at blood sample at the end of Week 2 to assess lamotrigine levels and a blood sample for determination of the 583C80 metabolite at the Month 6 visit or premature discontinuation (whichever came first). For the subjects previously in LAM20006, regular clinic visits and assessments were performed at 4-2week intervals throughout the study.

Treatment scenario 1: For subjects who reached their optimal LAMICTAL dose in LAM20006 and entered LAM20007 from the optimization period of the OLP of LAM20006 or were randomized to LAMICAL in the DBP of LAM20006 and either completed this phase or met escape criteria, these subjects began LAM200007 on a LAMICTAL dose considered to be appropriate by the investigator. Investigators had the flexibility to increase/decrease the dose of LAMICTAL within the dosing guidelines as clinically required.

Treatment Scenario 2 applied to subjects who received placebo in LAM20006 DBP and met escape criteria before the LAMICTAL dose was reduced to zero or met escape criteria after receiving 100% placebo for less than 2 weeks. Subjects who were receiving 75%, 50%, 25% or 0% (for less than 2 weeks) of LAMICTAL at the time of escape from LAM20006 could begin LAMICTAL in LAM20007 at doses of no more than 100%, 75%, 25% respectively, of their optimal dose. The dose was to be maintained for 1 week and then increased in weekly increments in accordance to Treatment Scenario 3, starting with the post Week 4 dose increments.

Treatment scenario 3 applied to LAMICTAL-native subjects or subjects who received 100% placebo and 0% LAMICTAL for more than 2 weeks in the CPB of LAM20006. The dose initiation and escalation schedule was as follows:

- LAMICTAL added to Non-EIAEDS or VPA

  Week 1 and 2: 0.15mg/kg/day

  Week 3 and 4: 0.3mg/kg/day

  Maximum increments after Week 4 = 0.3mg/kg/day/week

  Maximum maintenance dose: 5.1mg/kg/day or 200mg/day.

To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 0.3 mg/day rounded to the nearest whole tablet and added to the previously administered dose.

- LAMICTAL added to EIAEDS

  Week 1 and 2: 0.6mg/kg/day

  Week 3 and 4: 1.2mg/kg/day

  Maximum increments after Week 4 = 1.2mg/kg/day/week

  Maximum maintenance dose: 15.6mg/kg/day or 400mg/day

To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 1.2 mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

For all treatment scenarios, the dose of LAMICTAL could be increased according to Scenario 3 post Week 4 increments until the subject reached an optimal clinical benefit that, in the opinion of the investigator, maximized seizure control and minimized adverse events. Once a subject achieved LAMICTAL dose optimization, the dose could be increased or decreased as clinically required. Subjects receiving VPA or non-EIAEDs could be titrated to a maximum maintenance dose of 10.2 mg/kg/day and subjects receiving EIAEDs could be titrated to a maximum maintenance dose of 30 mg/kg/day with GSK medical advisor approval.

A serum sample was taken from each subject at the end of Week 2. If the lamotrigine concentration in this sample was higher than 0.41 µg/ml, the concentration found in adults at Week 2, the subsequent doses for this subject during the dose escalation phase were reduced as described in the OCP review of Study LAM20006.

The background AED doses were to be kept as constant as possible during dose escalation. LAMICTAL-naïve subjects on 3 background AEDs at screen were tapered off of one AED while simultaneously beginning LAMICTAL dose escalation. However, the AED that was discontinued during dose escalation could not have changed the subject's enzyme induction status. Background AEDs could not be added during dose escalation. When subjects reached an optimal maintenance dose of LAMICTAL, there were no restrictions with regard to AED therapy with the exceptions of VPA and felbamate. If the subject was taking VPA as a background AED, then it could be the only background AED used. Felbamate could not be used during the study.

PK Sampling

In the LTG-naïve group, one blood sample was obtained at Week 2 for the purpose of individual titration, with the potential for an additional sample 2 weeks later if dose adjustment was necessary. An additional single blood sample was also collected in all LTG-naïve subjects at the 6-month visit for quantification of the metabolite 583C8 and to determine serum lamotrigine level.

Blood and saliva samples were collected from consenting LTG-naïve subjects at approximately Week 5 to determine PK parameters after three times daily dosing had been achieved and doses of LTG had been unaltered for 7 days for subjects on EIAEDs or 14 days for subjects on non-EIAEDs. Blood and saliva were collected at pre-dose and at 1, 2, 3, 4, 6, and 8 hours after the

dose. If it was not possible to obtain all of the blood samples, saliva samples at all time points and blood samples at pre-dose, 2, and 6 hours post-dose were collected.

Inclusion criteria for previous LAM20006 subjects include completion of the OLP of LAM20006, with screening assessments acceptable to the investigator. Inclusion criteria for LAMICTAL naïve subjects include male or female pediatric subject between the ages of 1-24 months old at the time of study entry, with a history of ≥ 4 reliably detectable recurrent partial seizures per month, with seizures uncontrolled by at least one other AED whose plasma concentrations were within the acceptable ranges for therapy if a therapeutic range has been established for the AED. Subjects on non-EIAEDs (including VPA) must have weighed at least 6.7 kg at study entry. Exclusion criteria included any condition that may affect absorption, distribution, metabolism, or elimination of drugs and prevents effective use of LAMICTAL. Exclusion criteria for LAMICTAL-naïve patients included being on a maintenance regimen of more than 2 background AEDs (unless the third is tapered and discontinued during LAMCITAL dose escalation without changing the enzyme induction status, taking VPA with one or more additional AEDs, or taking VPA for < 6 months or > 6 months and has evidence of hepatic dysfunction.

ASSAY:

Table 2. Performance of Analytical Methods for Lamotrigine study LAM20007

Analyte	Method	Calibration Standards (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Lamotrigine (Serum)	LC/MS/MS	4-4000 ng/ml	r > 0.994	4.0 ng/ml	12.0	5.6	0.7
					1600.0	3.2	-0.7
					3200.0	3.7	-0.8
Lamotrigine (Saliva)	LC/MS/MS	4-4000 ng/ml	r > 0.994	4.0 ng/ml	12.0	6.8	-2.9
					1600.0	5.8	-0.5
					3200.0	3.8	1.4
583C80 * (serum)	LC/MS/MS	4-500 ng/ml	r > 0.996	4.0 ng/ml	12.0	7.2	1.6
					200	4.5	-2.7
					400	6.0	-3.1

*also referred to as metabolite GW313090

Serum and saliva samples were stored at -20º C until analysis. Each batch of samples was run against duplicate calibration standards (9 nonzero standards for lamotrigine and 8 for GW313090) along with triplicate QC samples. QC samples and calibration standards met acceptable criteria. Samples were analyzed from 12/17/03-1/16/06. The Sponsor states in an email of 3/21/07 that human serum and saliva lamotrigine PK samples were analyzed on an ongoing basis within their documented periods of frozen storage stability. The assay is acceptable.

RESULTS:

Demographics

A total of 206 subjects enrolled in the study; 117 completed the study at the interim cutoff in January 2006 and 135 had completed the study as of the final abbreviated clinical study report of

3/19/07 (safety update). A total of 204 subjects received at least 1 dose and were included in the safety population. Demographics in the Safety population are shown in the table below, as provided by the Sponsor. The youngest subject in the study was 2 months old.

Table 7 Demographic Characteristics (Safety Population: LAM20007)

	All Subjects N=204	LTG Experienced N=125	LTG Naive N=79
Mean Age (months) (SD)	15.9 (6.81)	17.4 (6.78)	13.4 (6.13)
Age Stratum, n (%)			
<6 months	16 (8)	4 (3)	12 (15)
6-12 months	52 (25)	27 (22)	25 (32)
>12 months	136 (67)	94 (75)	42 (53)
Gender, n (%)			
Female	90 (44)	58 (46)	32 (41)
Male	114 (56)	67 (54)	47 (59)
Race n (%)			
White	171 (84)	107 (86)	64 (81)
Black	9 (4)	6 (5)	3 (4)
Asian	2 (<1)	2 (2)	0
American Hispanic	14 (7)	6 (5)	8 (10)
Other	8 (4)	4 (3)	4 (5)
Mean Weight (kg) (SD)	9.5 (2.53)	9.4 (2.53)	9.5 (2.54)
Mean Height (cm) (SD)	73.6 (9.63)	73.4 (10.12)	73.9 (8.82)

LTG Experienced = LAMICTAL Experienced Subjects; LTG Naïve = LAMICTAL naïve subjects
Data Source: Table 6.4

There were 74 subjects in the PK population. In the < 6 months old group, there were 12 subjects who had some PK including 2 subjects with a full PK profile (note: there was only 1 child < 6 months old in the PK population in Study LAM20006). Based on the population PK data, the youngest PK subject was 2.4 months old at the time of PK.

A summary of presenting concomitant AED groups in Study LAM20007 is shown in the table below:

	All subjects (n=204)	**LTG Experienced (n=125)**	**LTG Naïve (n=79)**
Induced	120 (59%)	83 (66%)	37 (47%)
Non-Induced	62 (30%)	30 (24%)	32 (41%)
Valproic Acid only	22 (11%)	12 (10%)	10 (13%)

The most commonly used concomitant AEDs were the inducers phenobarbital (37%), carbamazepine (25%), phenytoin (7%), the inhibitor valproic acid (11%), and the neutral AEDs topiramate (15%), clonazepam (12%), vigabatrin (12%), oxcarbazepine (6%).

LAMOTRIGINE Exposure

The average total daily lamotrigine dose by concomitant AED group in the safety population in Study LAM20007 is shown in the table below, as provided by the Sponsor.

Table 11 Average Total Daily LTG Dose by Concomitant AED Group (Safety Population: LAM20007 Only)

		LTG TDD (mg/kg/day)			
AED Group	N	Mean	Median	Min	Max
Overall	204	8.3	6.4	0.1	28.1
Induced	120	11.1	10.8	0.9	28.1
Non-Induced	62	4.4	4.0	0.1	15.7
VPA Only	22	3.7	3.9	1.0	6.5

Data Source: Table 7.3

The mean total daily dose in the non-induced (neutral) group is approximately 19% greater than that in the VPA only group.

LAMOTRIGINE Pharmacokinetics

A total of 74 subjects at Week 2 provided serum LTG concentrations. These are presented in the table below, summarized by concomitant medication.

	Lamotrigine Concentration (µg/ml) in **Induced Subjects**	Lamotrigine Concentration (µg/ml) in VPA only subjects **(inhibitors)**	Lamotrigine Concentration (µg/ml) in Non-Induced Subjects **(Neutrals)**
Mean (% CV)	0.258 (77)	0.252 (51)	0.141 (103)
Range (ng/ml)	0.026-1.290	0.077-0.420	0.019-0.624
N	38	11	25

At week 2 sampling, 4 subjects in the inducing group, 1 subject in the valproic acid group, and 2 subjects in the neutral group had concentrations greater than 0.41 µg/ml. In 4 of those subjects, the concentrations exceeded the target concentration by < 0.1 µg/ml. Two of these subjects received higher doses than specified in the protocol.

Week 5 PK data

Noncompartmental PK parameters at Week 5 were derived in 15 subjects, the majority of whom (12/15) were taking EIAEDs. Results are shown below by concomitant AED classification.

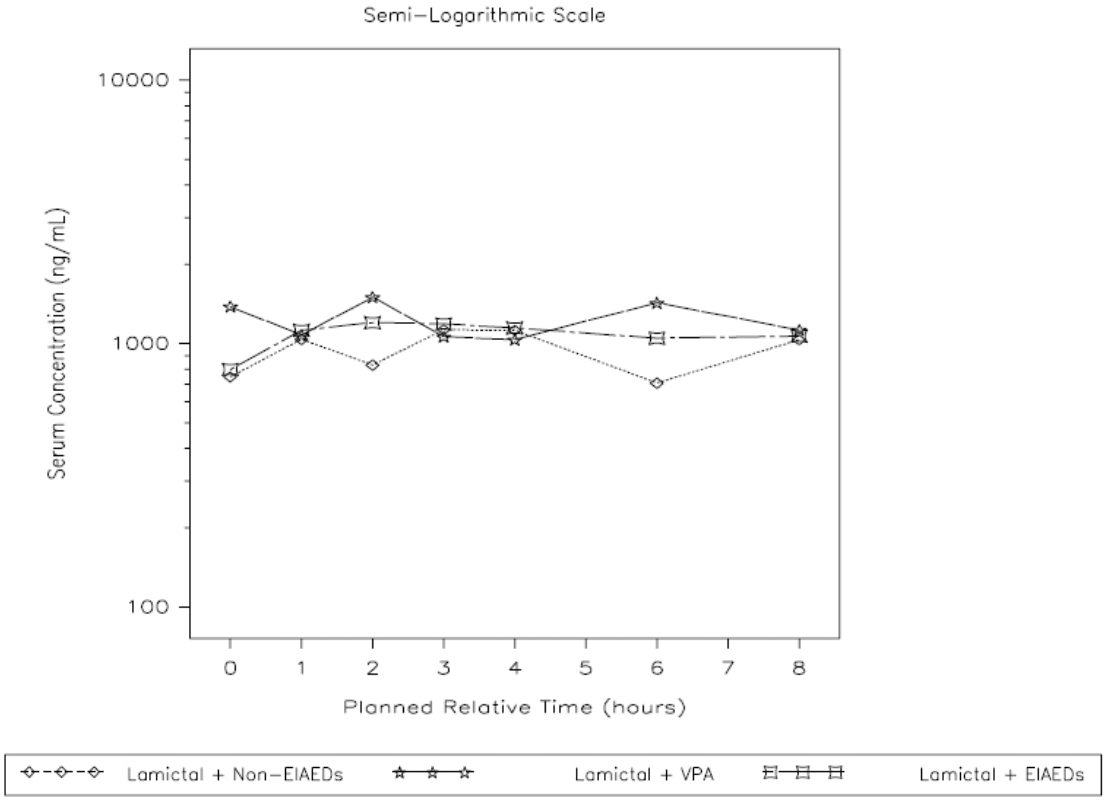
Week 5 PK Data in LAM20007 (mean, %CV)

	Enzyme Inducers (n=12)	**Valproic Acid** (n=1)	**Neutral** (n=2)
Tmax (hrs)*	3.31 (0.83-8.00)	6.0	2.49 (0.97-4.00)
Cmax (µg/ml)	1.44 (51)	1.13	1.16 (22)
AUC0-8 (µg*hr/ml)	8.24 (52)	8.53	8.38 (19)
Clss/F (l/hr)	1.25 (67)	0.469	0.506 (65)
Clss/F (ml/min/kg)	2.19 (52)	0.60	0.69 (39)
Cavg (µg/ml)	1.03 (52)	1.07	1.05 (19)

*median (range)

Six of the 15 subjects (5 inducers, 1 VPA) had profiles obtained on the same day that a new dose was administered prior to the PK sampling so that the PK parameters do not necessarily represent steady state.

The mean plasma-concentration time course profiles at Week 5 are shown in the figure below, as provided by the Sponsor.



The significant limitations (e.g number of subjects) in the traditional PK data set do not allow for conclusions to be drawn regarding comparisons between the different classes of concomitant AED.

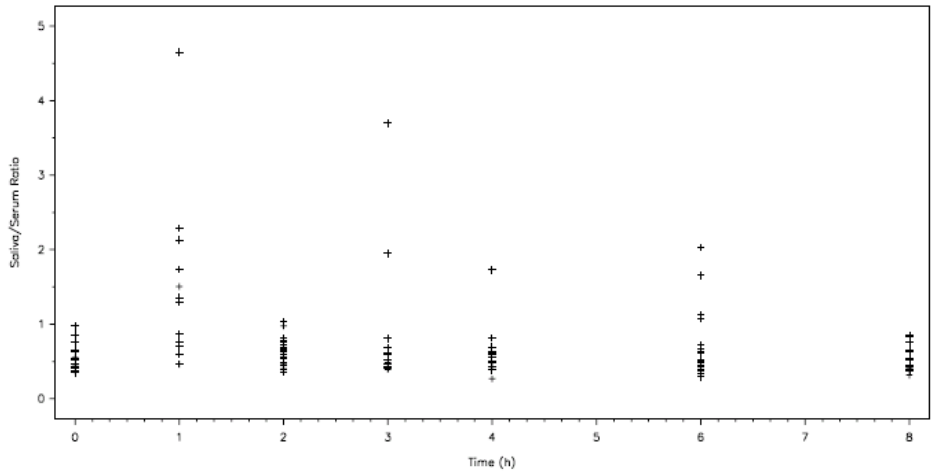
Saliva Lamotrigine PK at Week 5

Saliva LTG concentrations noncompartmental PK parameters were generated for 24 subjects, 19 of whom were taking enzyme inducers with lamotrigine. The results are summarized in the table below. Since these data along with data from LAM20006 suggest that saliva data do not accurately predict serum PK data, these data will not be further evaluated in this review.

Week 5 PK Saliva Data in LAM20007 (mean, %CV)

	Enzyme Inducers (n=11)	**Valproic Acid** (n=1)	**Neutral** (n=3)
Cmax (µg/ml)	2.17 (92)	2.57 (106), n=2	0.81 (74)
AUC0-8 (µg*hr/ml)	6.14 (34)	3.87	3.27 (49)
Cavg (µg/ml)	0.77 (34)	0.48	0.41 (49)

Figure 9.6
Scatter Plot of Saliva/Serum Ratio versus Time at Week 5/6



Serum 583C80 Concentrations during the Maintenance Phase
583C80 was below the LLQ of the assay in all samples that were obtained for this purpose in LAM20007.

PK at End of Maintenance (>Week 9)

Serum lamotrigine concentrations were provided by 67 subjects during the Maintenance Phase (Week > 9). Concentrations in subjects taking valproic acid are, on average, higher than concentrations in the other 2 groups following dosing optimization. Concentrations in the induced group are similar to those in the neutral group.

	Lamotrigine Concentration (µg/ml) in **Induced Subjects**	Lamotrigine Concentration (µg/ml) in VPA only subjects **(inhibitors)**	Lamotrigine Concentration (µg/ml) in Non-Induced Subjects **(Neutrals)**
Mean (% CV)	2.954 (68)	5.685 (60)	3.015 (63)
N	33	11	23

Pharmacodynamic Analysis

Approximately 62% of subjects in the ITT population experienced a ≥50% reduction from baseline in partial seizure frequency. The median reduction in partial seizure frequency in the induced AED group was 76.6%, in the non-induced group was 66.5%, and in the VPA group was 64.5%., according to Table 19 in the Sponsor's study report.

Safety

Safety results will not be reviewed in detail by OCP. Briefly, the Sponsor states that 87% of subjects experienced AEs. The most common AEs included pyrexia (45%), upper respiratory tract infection (28%), ear infection (22%), cough (19%), vomiting (18%). Rash was reported in 13%. Treatment related adverse events, according to the Sponsor, that occurred in greater than 1 subject included irritability (5%), rash (2%), somnolence (1%), insomnia (1%), constipation (< 1%) and decreased appetite)< 1%).

Thirty-four percent of subjects experience serious adverse events, including 7 subjects who died. The most common serious adverse events included pneumonia, complex partial seizures, and status epilepticus. Three subjects were prematurely discontinued from study drug due to rash. One subject reported rash that was considered to be a SAE but that subject did not discontinue the study due to rash.

Twenty-two subjects developed clinically significant abnormal treatment-emergent ECG abnormalities that included sinus bradycardia, sinus tachycardia, right axis deviation, atrial premature beats, right ventricular hypertrophy, and bi-ventricular hypertrophy.

CONCLUSIONS:

The conclusions from a clinical pharmacology perspective are as follows:

- The significant limitations (e.g number of subjects) in the traditional PK data set do not allow for conclusions to be drawn regarding comparisons between the different classes of concomitant AED. However, as previously observed in other studies, the apparent oral clearance appears to be lower in the valproic acid and neutral groups than in the enzyme inducer group at 5 weeks.
- The mean average total daily lamotrigine dose for the neutral group was approximately 19% greater than that of the valproic acid group.

4.2.6 POPULATION PK ANALYSIS

Pharmacometrics Review

sNDA	20241/032
Submission Date(s)	
PDUFA Due Date	05/30/2007
Brand Name	Lamictal
Generic Name	Lamotrigine
Pharmacometrics Reviewer	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Primary Reviewer	Sally Yasuda, M.S., Pharm.D.
Primary Review Team Leader	Ramana Uppoor, Ph.D.
Sponsor	Glaxo Smith-Kline
Submission Type	sNDA
Formulation	Oral Chewable tablets

(b) (4)

Executive Summary

LAMICTAL™ is an AED structurally unrelated to other marketed AEDs and has been approved for add-on therapy of partial seizures in adults and pediatric subjects (above 2 yrs), and the generalized seizures associated with the Lennox-Gastaut syndrome. It has also been approved as (b) (4) conversion of lamotrigine add-on therapy to lamotrigine monotherapy in adults with partial seizures.

Current submission was aimed to compare the efficacy of LAMICTAL as add-on therapy versus placebo in subjects 2.4 to 25.8 months of age with partial seizures. This was an international, multi-center study consisting of an open-label period followed by a parallel, randomized, double-blind, placebo-controlled period. A total of 38 subjects were randomized in the Double- Blind Phase (19 per treatment group), while 177 subjects received open-label treatment with LAMICTAL.

The key finding of the present submission are:

- A one-compartment open model with 1st order absorption and elimination adequately describes the serum concentration time profile of lamotrigine in pediatric patients aged 2.4 – 25.8 months.
- Concomitant AEDs (Inducers and VPA) and body weight were found to be the major explanatory variable for the inter-individual variability associated with oral clearance of lamotrigine.
- The oral clearance of lamotrigine is increased by 80% when administered with glucuronidation inducing AEDs such as Phenytoin, Carbamazapine, Phenobarbital, etc.
- The oral clearance of lamotrigine is decreased by 70% when administered with VPA.
- Bodyweight accounts for the age-related effects on the oral clearance of lamotrigine.
- No attempts were made to explore the relationship between the exposure and the pharmacodynamic response. Such an analysis would have provided more insights regarding the effectiveness of Lamictal in the present population (2.4 month – 25.8 months), especially given the fact that the primary analysis did not reach pre-specified statistical significance.

Recommendation

- Explore dose/concentration-percent change in seizure frequency for all the patients in the open label phase using mixed modeling approach.
- Explore dose/concentration-percent change in seizure frequency for the 38 patients who entered the double blind phase. This analysis can utilize both the open label as well as the double blinded phase using mixed modeling approach.
- Further, compare the exposure-response relationship with that observed in older children and adults.
- Please provide the data for exposure – response analysis in the format described in Appendix 1.

Signatures:

Rajanikanth Madabushi, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Yaning Wang, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology

Table of Contents

List of Tables

List of Figures

(b) (4)

Introduction

LAMICTAL™ [lamotrigine; (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine] is an AED structurally unrelated to other marketed AEDs and has been approved for add-on therapy of partial seizures in adults and pediatric subjects (above 2 yrs), and the generalized seizures associated with the Lennox-Gastaut syndrome. LAMICTAL has also been approved as (b) (4) conversion of lamotrigine add-on therapy to lamotrigine monotherapy in adults with partial seizures.

In infants aged less than 24 months, there is minimal safety or pharmacokinetic data available for LAMICTAL. Studies LAM20006 and LAM20007 have been conducted to provide efficacy and long-term safety as well as pharmacokinetic data in this pediatric population (<24 months).

Sponsor's Analysis

Objectives

- To evaluate the population pharmacokinetics of lamotrigine in pediatric subjects aged 1 – 24 months.
- To explore the effects of the selected demographic and physiological factors on the population pharmacokinetic parameters lamotrigine in pediatric subjects aged 1 – 24 months.
- To evaluate the impact of inter-occasion variability on the population pharmacokinetic parameter CL/F, of lamotrigine in paediatric subjects aged 1-24 months.

Data

The population model was built using data from both studies (LAM20006 and LAM20007), which contained sparse and semi-intense profiles over a treatment duration of up to 6 months.

Study LAM20006

Study LAM20006 was a double-blind, placebo-controlled, add-on clinical trial of safety, pharmacokinetics and efficacy of LAMICTAL in pediatric age subjects (1-24 months). Open label LAMICTAL was added to an ongoing anti-epileptic drug (AED) regimen and titrated to an individual optimized dose (based on seizure control and minimum adverse events). A total of 177 subjects received open label LAMICTAL. During the open label/dose optimization phase of the study, dose titration depended upon a subjects background AEDs as follows:

<u>LTG added to VPA or non-EIAEDs</u>:
Week 1 and 2: 0.15mg/kg/day
Week 3 and 4: 0.3mg/kg/day

Maximum maintenance dose: 5.0 mg/kg/day or 200mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 0.3mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.

LTG added to EIAEDs (maximum of two)

Week 1 and 2: 0.6mg/kg/day
Week 3 and 4: 1.2mg/kg/day

Maximum maintenance dose: 15mg/kg/day or 400mg/day. To achieve the maximum maintenance dose, subsequent doses were increased every week by no more than 1.2mg/kg/day rounded to the nearest whole tablet and added to the previously administered dose.
A single blood sample was obtained at the end of Week 2 of this open label phase to assess the need for individualization of the dosing schedule. This sample was recommended to be taken mid-interval, so that it could be compared with the concentration in adults of 0.41 ug/mL. The recommended timing is summarized in **Table 1** below:

Table 1: Summary Table of Dosing Frequency and Recommended PK Sample Collection at Week 2 During Titration.

Dosing Frequency	Ideal Sample Collection
Three times daily	4 h after dose
Twice daily	6 h after dose
Once daily	12 h after dose
Once every other day	24 h after dose

An additional blood sample was obtained at the end of the optimization period in some subjects. In consenting subjects, intense sampling was performed at around week 5, following at least 7 days on the same dosing regimen. In these subjects, samples were obtained pre-dose and at 1, 2, 3, 4, 6 and 8 hours post-dose.

2.3.2 *Study LAM20007*

Study LAM20007 was an open-label, uncontrolled, long –term study to assess the safety of LAMICTAL in pediatric subjects previously enrolled in protocol LAM20006 and LAMICTAL-naïve subjects (1-24 months of age).
Dose titration and pharmacokinetic sampling was performed only in patients who were lamotrigine naïve, as described for LAM20006. A single-blood sample was obtained at the end of week 2 and then again at 6 months or at premature discontinuation. In consenting, LAMICTAL-naïve subjects, intense sampling was performed at approximately week 5, when the subject has achieved t.i.d. dosing and receiving unaltered doses of lamotrigine for at least 7 days. Subjects on VPA or a non EIAED (non-Enzyme inducing anti-epileptic drug) must have achieved t.i.d. dosing and been receiving unaltered doses of LAMICTAL for at least 14 days (approximately end week 6). Samples were obtained pre-dose and at 1, 2, 3, 4, 6 and 8 hours post-dose.

Methods

The population pharmacokinetic modelling was conducted using the NONMEM software (version 5.1, GloboMax, MD) within the OBIWAN interface and database (GSK Validated system).
Graphical evaluation and statistics were performed utilizing SPLUS and Excel.
The pharmacokinetics of lamotrigine has been demonstrated in both adults and children to be adequately described by a one-compartment, first order absorption, linear elimination model. The published base model was applied to the sparse and intense data obtained in these two studies, to ascertain whether a reasonable description of the data using the underlying structural model was achieved.
The pharmacokinetic data were fitted using the NMTRAN subroutine ADVAN2 TRANS 2, with the first-order conditional estimation with interaction method within NONMEM.
Model acceptance was based on successful minimization, covariance step completion, number of significant digits >3, lack of correlation between pharmacokinetic parameters (<0.95), precision of parameter estimates (<30 %), combined with unbiased diagnostic plots (population predicted vs. observed concentrations, individual predicted vs. observed concentrations, weighted residuals versus observed concentrations and weighted residuals versus time after dose.
Different error models were explored/evaluated for both the inter-individual and random residual variability. These were assessed by graphical exploration of the distribution of the individual predicted Bayesian parameter estimates generated during the posthoc step, as implemented within NONMEM. The residual error model was assessed by both the graphical evaluation of the residual /weighted residual plots combined with precision in estimates of each component.
Inter-occasion variability on CL/F was also evaluated in the base model to test whether there was a decrease in the inter-individual variability, including the reliability of the characterization of the distribution as well as a decrease in the objective function, along with improvements in the diagnostic plots and parameter estimates.
The covariance between clearance (CL/F) and volume (V/F) was also evaluated using the BLOCK (2) attribute within NONMEM. Inclusion in the model relied on a significant decrease in the objective function, a successful minimization and maintained precision of PK parameters and correlation coefficients.
The overall quality of the “base-model” in terms of precision and bias was calculated and comparisons made with later models which incorporated covariates as well as a comparison with the published structural literature model.

Covariate Analyses

The covariates considered for evaluation of their contribution to the overall variability in CL/F and V/F of lamotrigine in this pediatric population were post-natal age (months), height/length (cm), weight (kg), gender (male or female), race (white, black, asian, American hispanic, other), body surface area, AED medication, non-AED medication, serum creatinine and estimated creatinine clearance. Estimated creatinine clearance was determined according to the Schwartz equation.
Concomitant use of AEDs was classified as follows:

Enzyme inducers:	Typically carbamazepine (CBZ), phenytoin (PHT), phenobarbital(PB)

VPA (Inhibitors): Valproic Acid or divalproex Sodium
Neutral: Neither an inducer or inhibitor.

Plots of individual posthoc estimates of CL/F and V/F versus each covariate were used to select meaningful covariates and form for inclusion in the pharmacokinetic model. The effect of categorical covariates (e.g. gender (1,2), sex = 0 for male and 1 for female) was entered in the model in the general form:

$$CL / F = \theta 1 * (1 - SEX * \theta 2)$$

The effect of a continuous covariate (e.g. weight) was evaluated for its influence on the population mean values as follows:

$$CL / F = \theta 1 * (1 - (Covariate - median\ value) * \theta 2)$$

A univariate analysis was performed in NONMEM. The covariate with the largest change in the objective function (assumed to be $\chi 2$ distributed) with one change in the degrees of freedom >3.84 (p-value <0.05) was introduced into the model to become Base Model 1. Evaluation of plots of the posthoc estimates of CL/F and V/F from Base Model 1 versus the remaining covariates was performed, to ascertain the form and relevance of the likely relationship. Each covariate was then added to the Base Model 1 individually. The covariate with the largest change in objective function when added to Base Model 1 which was >3.84, and lead to a reduction in the between subject variability on the parameter estimate to which it was added, as well as maintenance of precision of the fixed effects parameter estimates became Base Model 2. This step (including graphical evaluation) was repeated until no more significant changes in the objective function occurred on addition of the next covariate. The resulting model was considered to be the full model. The interaction between demographic covariates in the model build was also tested.
The relevance of the selected covariates on CL/F and V/F was subsequently evaluated by model breakdown, according to a stepwise procedure. If an increase in the objective function was observed on removal from the model $\Delta > 10.827$ (p-value ≤ 0.001), the particular covariate was not considered statistically relevant and removed from the model. The backward technique continued until all covariates in the model passed the criteria

Comparison with the published model and model refinement

The performance of the final model in comparison with the published model for older children was made by including anti-epileptic comedication classification into inducers, inhibitors and neutral. The precision and bias of the two models applied to this data set was evaluated. The impact of any differences in the covariate models was also assessed, in terms of bias, precision and clinical relevance.

Model exploration

Due to the limited data within the two studies (LAM20006 and LAM20007), and the lack of availability of external data sets, it was not possible/appropriate to perform an external validation or internal validation via withholding a sub-section of the data set and testing the ability of the models prediction of the independent data or subset. Therefore, model exploration was performed via simulation and prediction of different scenarios and subsets of the data set and titration of patients as follows:

1. Prediction of trough concentrations at week 5 for subjects on an 8h dosing schedule (per protocol), and were on a steady-state dosing regimen, separating by concomitant AED therapy (namely inducers, VPA or neutrals (neither an EIAED nor VPA)).
2. Prediction of Dose-Normalized AUC$(0\text{-}8)_{ss}$ at week 5, in those subjects who were on a steady-state dosing regimen, based on non-compartmental analysis results (reported elsewhere), separated by concomitant AED therapy (namely inducers, VPA or neutral (neither AIAED or VPA)).
3. Evaluation of dosing recommendations for the currently approved dosing recommendations (lamotrigine +VPA, lamotrigine + a non-inducing AED and not VPA or, lamotrigine+EIAED) based on week 2 concentrations.

Results

Demographics and other baseline characteristics

A total of 143 subject provided at least 1 evaluable PK concentration (with evaluable time data and associated dosing history). A total of 591 concentrations from the 143 subjects were obtained. A summary of demographic data using the information from the first observation in each subject in the population PK data set from studies LAM20006 and LAM20007 are presented in Table 2.
A summary of the different AED and hepatic enzyme effect are presented in Table 3. Overall classification was made according to Inducers, Inhibitors and Neutrals. Neutrals consisted of patients on drugs with no known inducer/inhibitor potential.

Table 2: Summary of Key Demographic Information from LAM20006 and LAM20007 individually and Combined in Subjects Using From 1st Observation.

Demographic	Study 20006	Study 20007	Combined
Gender	33 (M), 32(F)	47 (M), 31 (F)	80(M), 63(F)
Median Age (post-natal) months Week 2	14 (4.7 – 25.0) N=65	13.5 (2.4 – 25.8) N=78	13.7 (2.4 – 25.8) N=143
Weight (kg)	9.8(5.5 – 14) N=65	9.5(3.00 – 16.8) N=78	9.5 (3.00 – 16.8) N=143
Body Mass Index(kg/m^2)	16.7(12.6 -31.9) N= 65	16.8 (12 – 22) N=78	16.7 (12 – 31.9) N=143
Estimated Creatinine Clearance (ml/min)	128 (61 – 325) N=65	139 (69 – 216) N=78	131(61 – 325) N=143
Race: 1=Caucasian 2=Black 3=Asian 4=American Hispanic 5=Other	1(N=58) 2(N=4) 3(N=0) 4(N=2) 5(N=4)	1(N=63) 2(N=3) 3(N=0) 4(N=8) 5(N=4)	1(N=121) 2(N=7) 3(N=0) 4(N=10) 5(N=5)

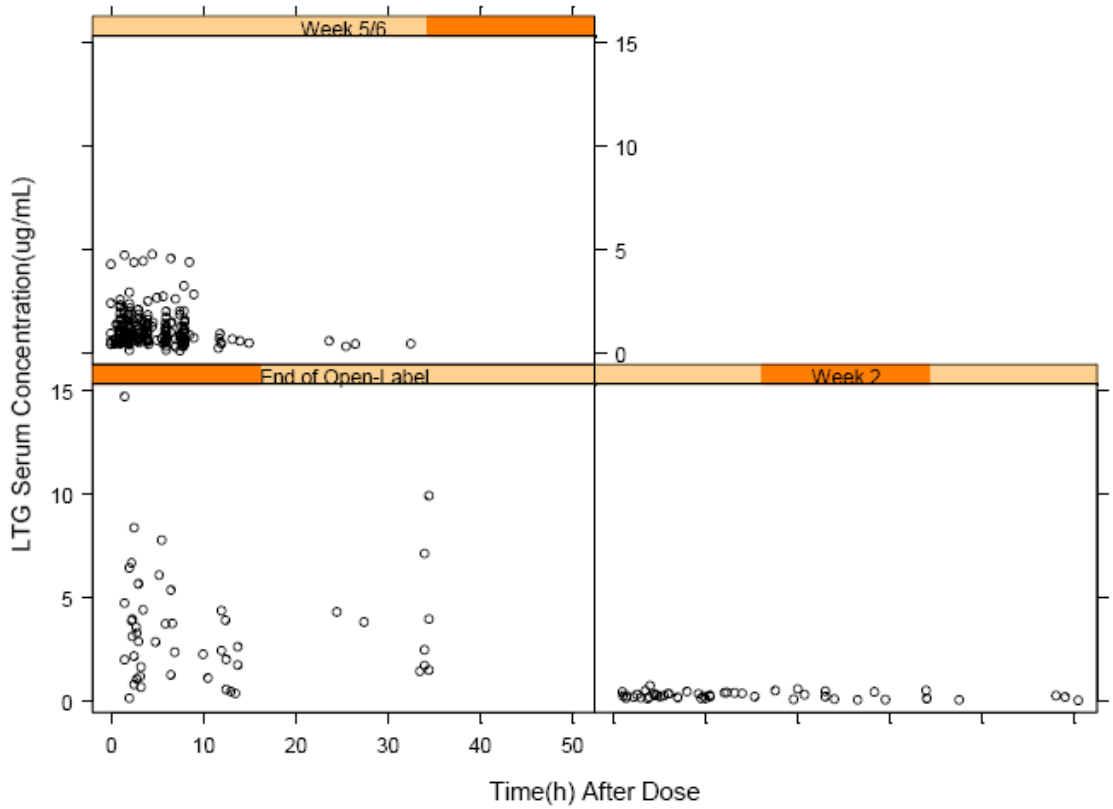
Table 3: A summary of the different AED abbreviations and hepatic enzyme effect are presented

Inducer Status	Study 20006	Study 20007	Combined
Inducers	37	40	77
VPA	12	12	24
Neutral [1]	16	28	44

1. In the population data set, one patient (ID=7534, STUDY=LAM20007) received VPA and Phenobarbital. Due to the interacting nature in opposite directions with Lamotrigine, was categorized as a neutral.

The observed lamotrigine serum concentration data versus time after dose on Weeks 2, 5/6 and at the end of the optimization period in LAM20006 is presented in Figure 1. The concentration range at week 2 in neutrals subjects was 0.041-0.493 µg/mL, and 0.182 - 0.561µg/mL in patients on VPA and 0.020-0.732 µg/mL in subjects on enzyme inducing AED therapies. The concentration range during the optimization/end of open label phase was 0.126-8.35 µg/mL in neutral subjects, 0.654 -14.7 µg/mL in patients on enzyme inhibitors and 0.384 -7.75 µg/mL on enzyme inducing AED therapy.

Figure 1: Summary Plot of LTG Serum Concentrations (ug/mL) versus Time (h) After Dose Separated by Assessment Period, Week 2, Week 5/6 and End of Open-Label (Study Protocol: LAM20006)



The observed LTG serum concentration data versus time after dose on Weeks 2 and 5/6 and at 6 months (or at premature drop-out) in LAM20007 are presented in Figure 2 of this report. The concentration range at week 2 in neutral subjects were 0.019 – 0.62 µg/mL, 0.077-0.420 ug/mL in subjects on VPA and 0.026-1.29 µg/mL in subjects on enzyme inducing AED therapy.

Base Model

Consistent with literature and historical data, the pharmacokinetic data from both LAM20006 and LAM20007 were adequately described by a 1-compartment, Ist order absorption, and linear elimination model. It was possible to estimate inter-individual variability (IIV) on CL/F and V/F, which was introduced into the model as a log-normal distribution. However, despite the intense data at week 5/6 from both studies, it was not possible to get a reliable estimate of the IIV on the absorption rate constant ka. Evaluation of the data indicates that very little data was captured during the absorption phase, even when intense data was obtained in consenting subjects at week 5/6, where peak was obtained in many subjects by the first available sample time of 1 or 2 h postdose. Due to the limitations in the data set per se, inter-occasion variability (IOV) was not included in the base model or for further evaluation during the course of the model building. Residual error was best described by a combination of a proportional and additive error.

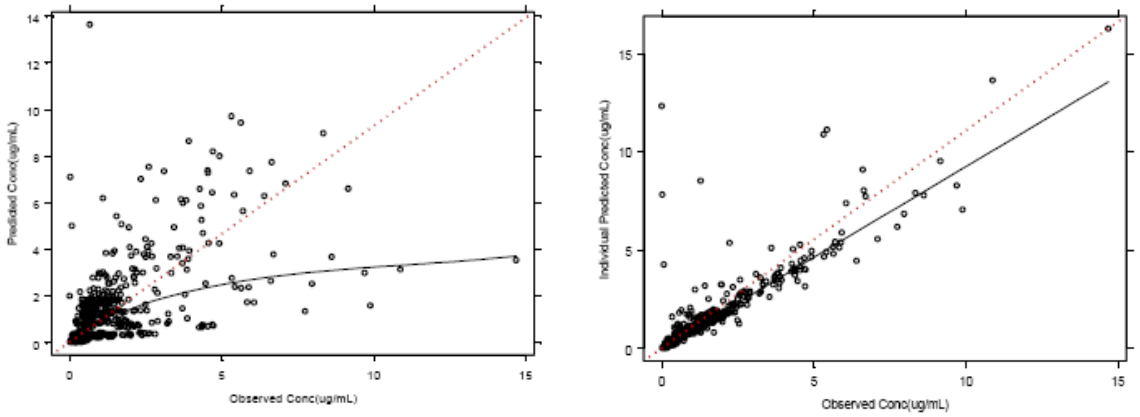
The population pharmacokinetic parameters obtained from the base model were reasonably well defined in respect to parameter precision (%RSE < 35%) with the exception of KA. The population means parameters and associated variability estimates are summarized in Table 5-1.

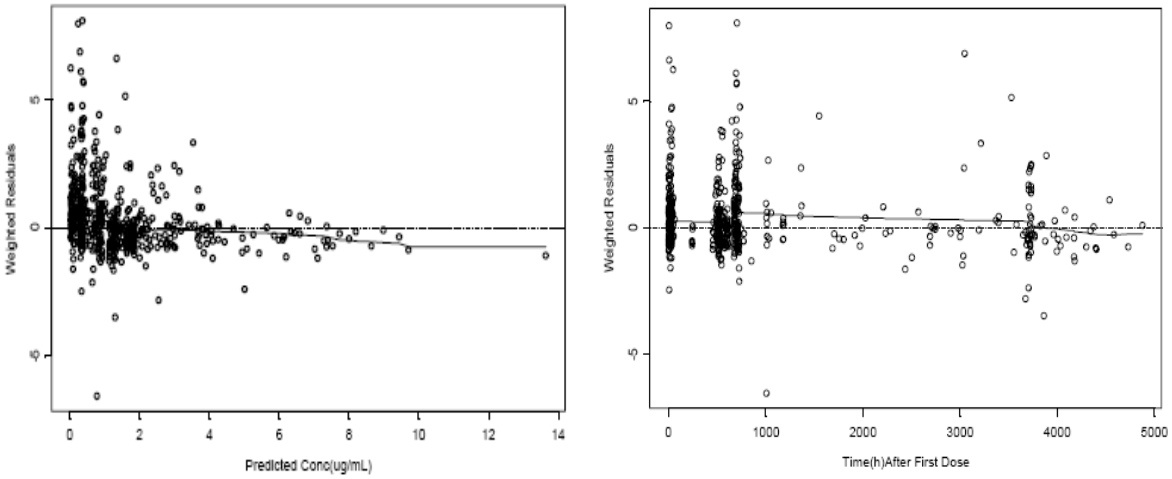
Table 4: Summary Table of the Population Mean Pharmacokinetic Parameter Estimates for the Base Model using FOCE with Interaction

	CL/F (L/hr)	V/F(L)	Ka(h^{-1})
Population Mean (95% CI)* %RSE	0.709 (0.62-0.80)* 6.61	33.8 (22.1 45.5)* 17.7	2.31 (0.154 -4.47)* 47.6
IIV %RSE	CV% =74.8 12.5 %	CV% =67.5 33.8%	
Residual Error	Proportional CV% =28% (%RSE=18.0%) Additive SD =0.06 ug/mL		
Objective Function	-505.46, %RSE=SE/Parameter*100 * (95% CI of FIXED Effect, calculated as population mean ± 1.96*SE)		

Overall, the goodness-of-fit plots represent a satisfactory description of the serum concentration data as shown in **Figure 2**.

Figure 2: Goodness-of-fit plots (Base Model)





Covariate Effects:

All available covariates, other than Race (due to the limited number in the groups) were numerically evaluated on CL/F, with all demographic covariates evaluated on V/F. The most significant covariates observed in the univariate analysis were inhibitors, inducers, weight and post-natal age. Little or no change in the objective function was observed when the relationship between V/F and any of the demographic covariates was evaluated, which was also consistent with graphical evaluation.

The covariate modelling was then progressed by forward (stepwise) addition of covariates to the model resulting in a full model of the form:

$$CL/F = \theta_1 * (1 + INH * \theta_4 + IND * \theta_6) * (1 + (WT - 9.5) * \theta_5 + (PAGE - 13.6) * \theta_7) * (1 - SEX * \theta_8)$$

$$V/F = \theta_2$$

$$KA = \theta_3$$

A summary of the model building is outlined in **Table 5**.

On attainment of the full model, a step wise covariate exclusion procedure was performed to remove factors that did not reach clear statistical significance, as assessed by a more stringent criterion for the changes in the objective function. This was achieved by taking the full model (Base Model 5) and setting each covariate to zero in turn, and the increase in the objective function was evaluated. An increase in the objective function of > 10.84 (p-value ≤ 0.005) allowed a covariate to be maintained in the model.

Table 5: Summary table of covariate build.

Model Number	OBIWAN Number	Description/Form	Obj Func	Δ Obj Func	Comments
1.6	173	Base Model IIV on CL/F and V/F	-505.462	-	IIV on CL/F and V/F.
2.7	27	Base Model 1 Inhibitors on CL/F	-575.17	-69.708	~74 % decrease in CL/F for inhibitors (Fixed Effect) 37% reduction in variance ω^2_{CL} 5.7% increase in variance ω^2_V
3.3	51	Base Model 2 Inhibitors and Weight on CL/F	-602.11	-26.94	11.7% change in CL/F per kg change from median CL/F (Fixed Effect) 2.21% reduction in variance ω^2_{CL} 1.87% reduction in variance ω^2_V
4.5	65	Base Model 3 Inhibitors, Weight and Inducers on CL/F	-631.98	-29.87	71% increase in CL/F for inducers from median CL/F (Fixed Effect) 20% reduction in variance ω^2_{CL} 13% reduction in variance ω^2_V
5.1	74	Base Model 4 Inhibitors, Weight, Inducers and Post-natal Age on CL/F	-644	-12.02	3% increase in CL/F per month change from median CL/F (Fixed Effect) 1.2 % reduction in ω^2_{CL} 5% increase in ω^2_V
6.1	96	Base Model 5 Inhibitors, Weight, Inducers, Post-natal Age, and Gender on CL/F	-648.89	-4.32	17% decrease in CL/F in females from median (Fixed Effects) <2 % reduction in ω^2_{CL} No reduction in ω^2_V
6.1	96	Full Model=Base Model 5	-648.89		

Only the effect of gender on CL/F lead to an increase of <10.84 to lead to breakdown model 1. Setting the effect of each covariate in break-down model 1, showed an increase in the objective function of >10.84 for all covariates. Hence Base Model 4 was the covariatel model which included: Inhibitors, Weight, Inducers and Post-natal age on CL/F. The effect of these covariates on model parameters expressed by the equations below:

$$CL/F = 0.58*(1-0.694*INH+0.711*IND)*(1+(WT-9.5)*0.083+(PAGE-13.6)*0.027) \quad L/h$$

$$V/F = 33.1 \quad L$$

$$KA = 2.09\ h^{-1}$$

The summary of the pharmacokinetic parameters of the covariate model is shown in **Table 6**.

Table 6: Summary of population mean pharmacokinetic parameters for the covariate model

		Effect of Inhibitors	Effect of Weight	Effect of Inducers	Effect of Post-natal age	IIV
CL/F(L/h) (95% CI) %RSE	0.580 (0.48 – 0.68)* 8.41 %	-0.694 (-0.78- -0.61)* 6.0 %	0.083 (0.045 - 0.12)* 23.4 %	0.711 (0.39-1.03) 22.9 %	0.027 (0.01-0.04)* 30.5 %	CV% =49.4 (%RSE=22.7)
V/F(L) 95% CI %RSE	33.1 (22.2 – 44.0) 16.7 %	not tested	N.S.	not tested	N.S	CV%=65.7 (%RSE=28.5)
KA	2.09 (0.36 -3.82) 42.2 %	-	-	-	-	-

Residual Error: Proportional Error CV% =30.3 (15.2 %), Additive SD = 0.013 ug/mL (LOQ=0.004 ug/mL)
Objective Function: -644.283,
%RSE=SE/Parameter Estimate*100,
*(95% CI of FIXED Effect, calculated as population mean ± 1.96*SE)
Source Data: OBIWAN Model 179
N.S.: not significant (p<0.05)

After completion of the model build, an error was determined in the data set where one subject had been coded as having “neutral” AED therapy, but review of source data highlighted that the patient was receiving VPA as their AED therapy in conjunction with LAMICTAL. The base and final model were rerun, and all results and comparisons presented from this point are based on the evaluation of the final revised data set.
A summary Table of the results from the covariate model rerun with the revised data set is presented below in **Table 7**.

Table 7: Summary of population mean pharmacokinetic parameters for the covariate model for the revised dataset

		Effect of Inhibitors	Effect of Weight	Effect of Inducers	Effect of Post-natal age	IIV
CL/F(L/h) (95% CI) %RSE	0.608 (0.52 – 0.69)* 7.27 %	-0.721 (-0.79- -0.65)* 5.0 %	0.083 (0.048 - 0.12)* 21.6 %	0.638 (0.36- 0.92)* 22.6 %	0.026 (0.01-0.04)* 29.8 %	CV% =46.1 (%RSE=21.6)
V/F(L) 95% CI %RSE	33.3 (22.4 – 44.2) 16.7 %	N.S.	N.S.	N.S	N.S	CV%=65.7 (%RSE=28.0)
KA	2.14 (0.31 -3.97) 43.6 %	-	-	-	-	-

Residual Error: Proportional Error CV% =30.4 (15.2 %), Additive SD = 0.013 ug/mL (LOQ=0.004 ug/mL)
Objective Function: -658.949,
%RSE=SE/Parameter Estimate*100
*(95% CI of FIXED Effect, calculated as population mean ± 1.96*SE)
Source Data: OBIWAN Model 400
N.S.: not significant (p<0.05)

The covariate model incorporates the effects of both weight and post-natal age. Since both of these factors are highly correlated (see **Figure 3**), a further numerical evaluation

of the relative contribution of post-natal age to the estimate of CL/F was performed looking at the extremes of weight and post-natal age, to determine whether any model refinement could be achieved. Addition of post-natal age in addition to weight on CL/F did not reduce the variance estimate of IIV on this parameter, therefore added no overall benefit/improvement to the model other than a reduction in the overall objective function. Hence a simpler model was thought to be more clinically appropriate and consistent for application. Therefore, using a refined final model that was consistent with already established pediatric administration incorporating weight and concurrent AED therapy on CL/F to make dose adjustments in this population was more appealing. A summary of the refined model parameters is provided in .

Figure 3: Correlation between Body Weight (Kg) and Post-Natal Age

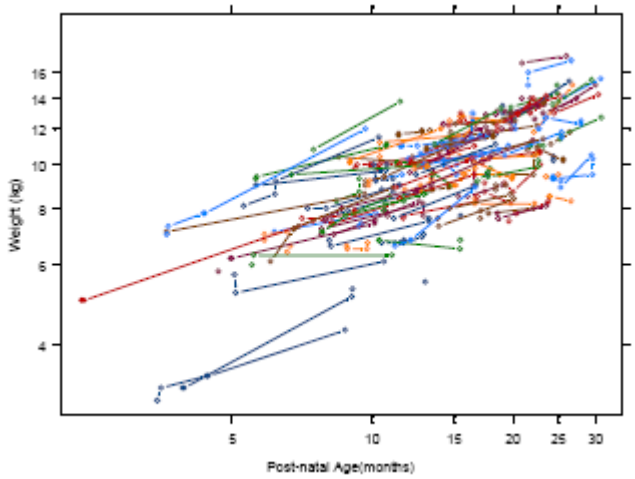


Table 8: Summary Table of Final/Refined Model Parameters using Revised Data Set

		Effect of Inhibitors	Effect of Weight	Effect of Inducers	IIV
CL/F(L/h) (95% CI) %RSE	0.614 (0.52 – 0.71)* 7.62 %	-0.708 (-0.78 - -0.64)* 5.23%	0.129 (0.11 -0.15)* 6.53 %	0.64 (0.36-0.93)* 22.4 %	CV% =46.7 (%RSE=22.6)
V/F(L) 95% CI %RSE	32.9 (22.3– 43.5) 16.4 %	not tested.	N.S.	not tested	CV%=64.2 (%RSE=30.5)
KA	2.25 (0.1-4.41) 48.9	-	-	-	-

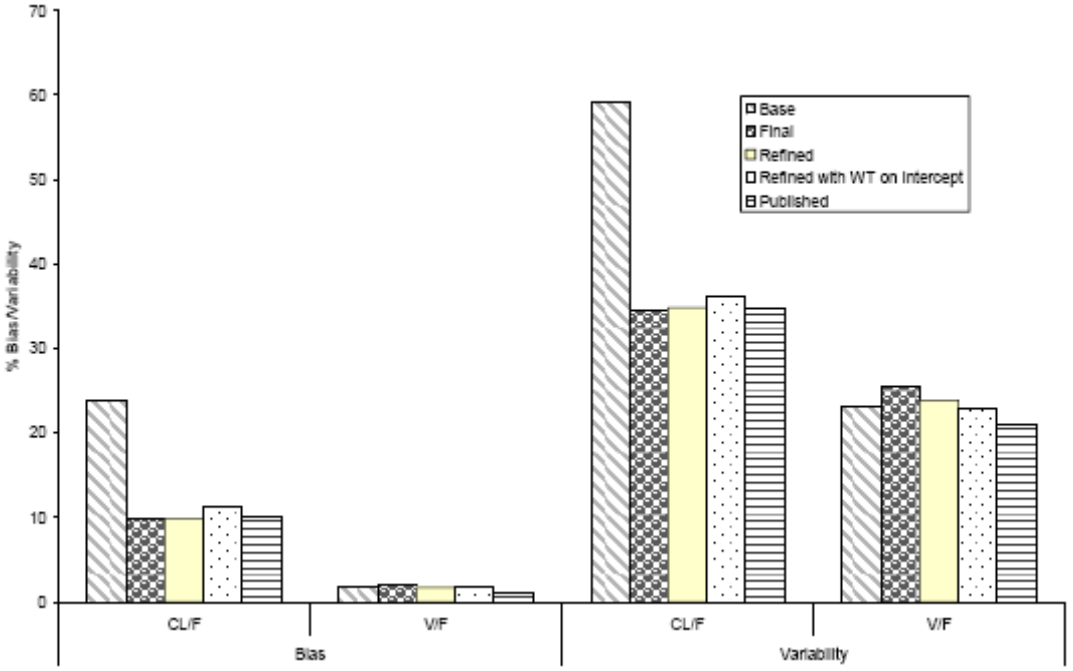
Residual Error: Proportional Error CV% =30.7 (15.1 %), Additive SD = 0.014 ug/mL (LOQ=0.004 ug/mL)
Objective Function: -646.135,
%RSE=SE/Parameter Estimate*100
*(95% CI of FIXED Effect, calculated as population mean ± 1.96*SE)
Source Data: OBIWAN Model 406
N.S.: not significant (p<0.05)

Model Performance

When the published model for older children (greater than 2 years) was applied to the data in this younger population and parameters estimated, an overall increase in the

objective function of 10.2 in comparison to the final model was observed (despite an increase in the degrees of freedom). A summary of the comparisons of the two models, with the base model (rerun with the revised data set) as a reference, in terms of bias and variability is presented in **Figure 4**. Comparison with the refined model (post-natal age removed), with and without weight on V/F is also presented for comparison purposes. A slight reduction in the bias and variability for the published structural model in terms of CL/F and in terms of bias for V/F were observed, in comparison to the covariate model. Removal of post-natal age from the covariate model established in this analysis, reduced both bias and variability on V/F and was similar to those of the published model. Introduction of weight or lean body mass on V/F in the refined did not improve the precision/variability to any significant level.

Figure 4: Performance of CL/F and V/F predictions of the Final Model with and without Post-Natal Age on CL/F and Published Structural Model (Revised Data Set).



Conclusion

Consistent with earlier evaluation of the pharmacokinetics of LTG in pediatrics and adults, the most significant factor affecting apparent clearance, CL/F, were AED therapy followed by weight.

On a weight adjusted basis, normalized mean clearances ranged from 0.55 -1.18 ml/min/kg (weight range 3 -16 kg) for subjects on neutral AED therapy, 0.16 -0.34 ml/min/kg (weight range 3-16 kg) for subjects on inhibiting AED therapy and 0.91 -1.94 (weight range:3-16 kg) ml/min/kg for subjects on inducing AED therapy.

The population mean estimate of lamotrigine volume of distribution was 32.9 L, with an inter-individual variability of 64%. No demographic covariates, including weight were found to explain the variability on this parameter.

Relationship between PK and PD parameters

No PK/PD analysis was performed using the data from this study.

Reviewer's Comments

- Even though the sponsor's final refined model is reasonable, the sponsor's approach for model development is solely based on statistical reasoning rather than clinical judgment. The prior information regarding the effects of various concomitant AEDs on the clearance of Lamictal from the adult and older children was not utilized as a part of the model building.
- No attempts were made to explore the relationship between the exposure and the pharmacodynamic response. Such an analysis would have provided more insights regarding the effectiveness of Lamictal in the present population (1 month – 24 months), especially given the fact that the primary analysis did not reach pre-specified statistical significance. Some of the analysis that sponsor could do are as follows:
    - Explore dose/concentration-percent change in seizure frequency for all the patients in the open label phase using mixed modeling approach.
    - Explore dose/concentration-percent change in seizure frequency for the 38 patients who entered the double blind phase. This analysis can utilize both the open label as well as the double blinded phase using mixed modeling approach.
    - Further, compare the exposure-response relationship with that observed in older children and adults.

Reviewer's Analysis

Objective

- The focus of the analysis was aimed at characterizing the pharmacokinetics of lamictal in pediatric patients aged 1 – 25.8 months.
- To explore the exposure – response of lamictal in pediatric patients aged 2.4 – 25.8 months.

Data

The population pharmacokinetic model was built using data from both studies (LAM20006 and LAM20007), which contained sparse and semi-intense profiles over a treatment duration of up to 6 months. The dataset (POPPK.xpt) for the analysis was provided by the sponsor with the submission dated 11/29/2006. The concentration data was log-transformed and analyzed.
Partial seizure counts in 4 week increments for the open label phase was available in the database and was utilized as the response for exploring exposure-response.

Method

The population pharmacokinetic modelling was conducted using the NONMEM software (version 5.1, GloboMax, MD) within the Wings for NONMEM interface.
Graphical evaluation and statistics were performed utilizing SPLUS and Excel.
The pharmacokinetic data were fitted using the NMTRAN subroutine ADVAN2 TRANS 2, with the first-order conditional estimation NONMEM. Graphical evaluations were performed utilizing SPLUS.

The effect of categorical covariates (e.g. IND (0,1), IND = 0 for non-inducing concomitant AED and 1 for inducing concomitant) was entered in the model in the general form:

$$CL/F = \theta_1 \bullet \left(1 - \left(IND \bullet \theta_2\right)\right)$$

The effect of a continuous covariate (e.g. weight (WT)) was evaluated for its influence on the population mean values as follows, where the median weight is 9.5 kg:

$$CL/F = \theta_1 \bullet \left(\frac{WT}{9.5}\right)^{\theta_2}$$

The inter-individual variability associated with the pharmacokinetic parameters was assumed to follow log-normal distribution.
The exposure-response of lamictal was graphically explored in the open label phase of the trial. Using the dosing history in the open label phase, average daily doses for 4-week increments of the open label phase were derived. The equation for population clearance derived for the population pharmacokinetic modeling was utilized to derive the average steady-state concentrations fotr the average daily dose was derived and

plotted against the percent change from baseline of partial seizures for 4-week increments.

Results

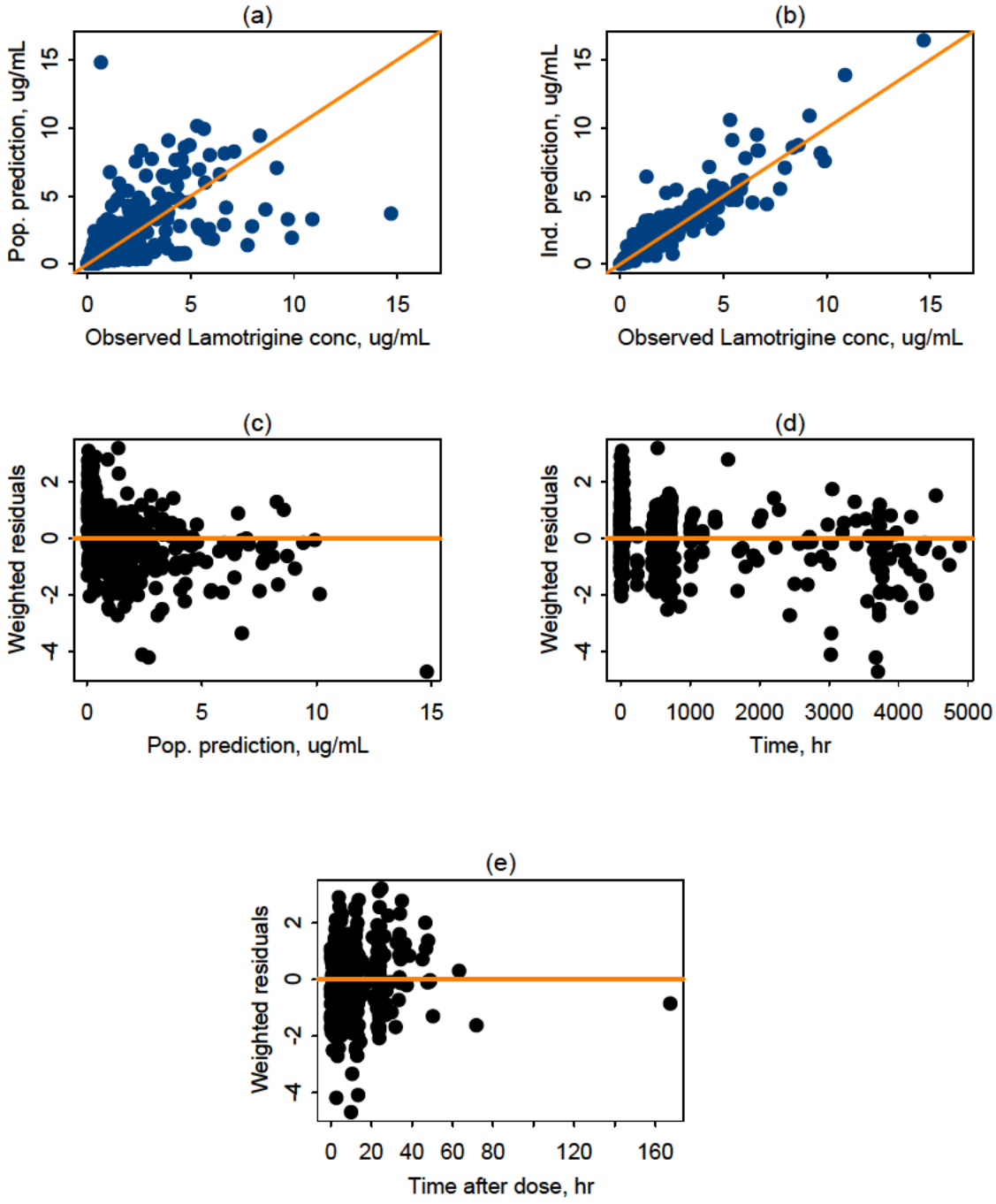
Population Pharmacokinetics

Population PK model was developed aimed at characterizing the pharmacokinetics of lamotrigine in pediatrics aged 2.4 – 25.8 months and to identify the key covariates. Log-transformation of the concentration data was performed to reduce model instability. A one compartment open model with first order absorption and elimination described the concentration-time profile of lamotrigine.

- Overall, the goodness-of-fit plots show that a one-compartment open model adequately describes the concentration-time profile in pediatric patients.

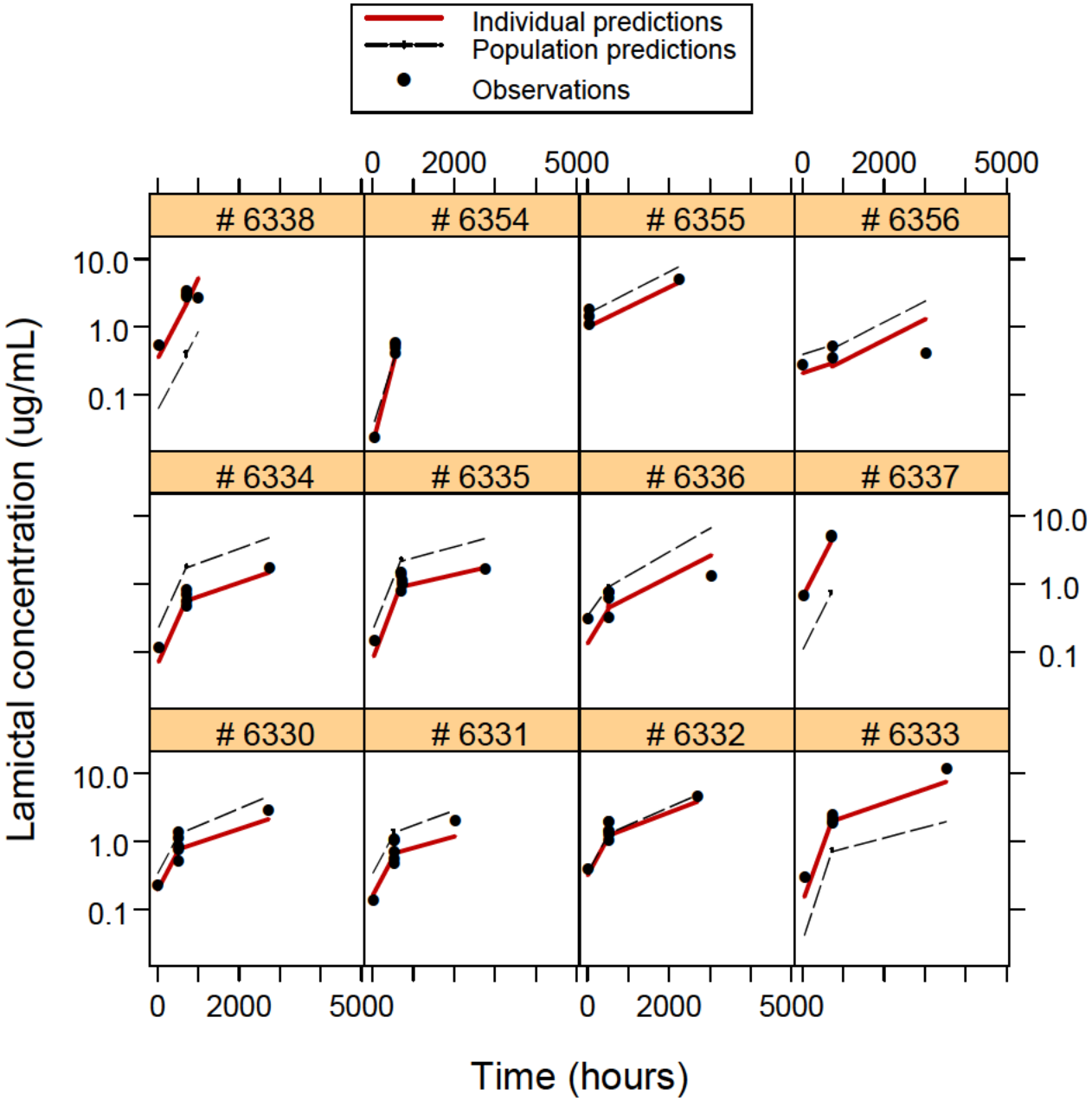
Figure 5).

Figure 5: Diagnostic plots show that a one-compartment model with 1st order absorption adequately describes lamotrigine concentration- time data.



- Individual plots represent a satisfactory description of the serum concentration-time data as shown in **Figure 6**.

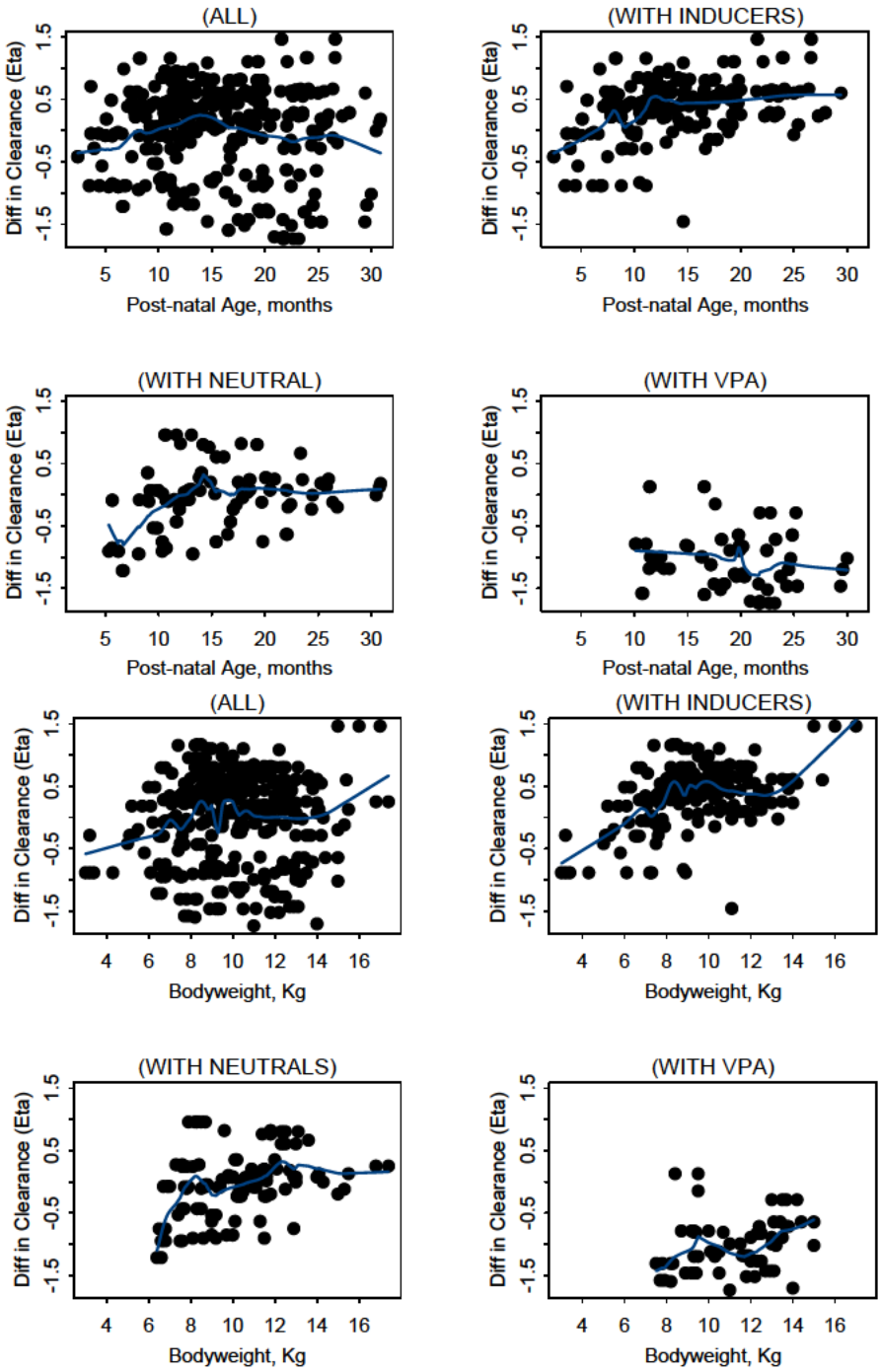
Figure 6: Representative individual concentration-time profiles.

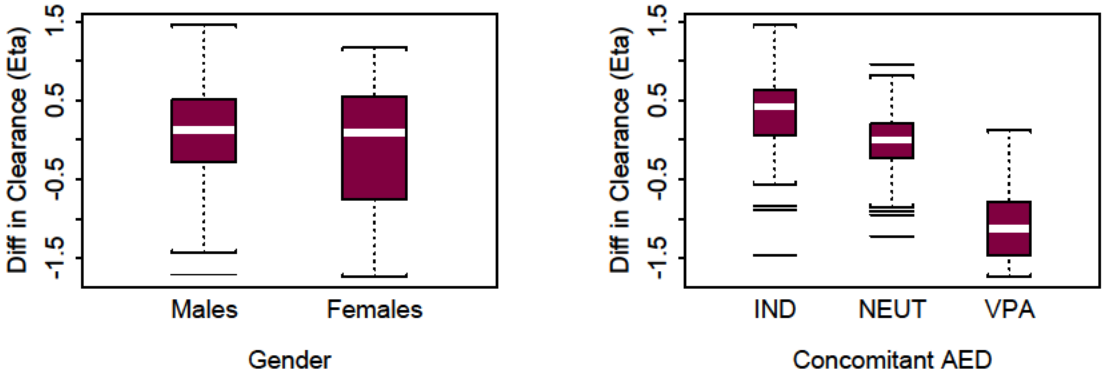


- Concomitant AEDs as indicated by Inducers (IND), Inhibitors (VPA) were identified as potential covariates on CL/F based on exploratory graphical analysis (Figure 7). Though body weight (WT) and post-natal age (PAGE) did not show

any relationship, however, within the individual concomitant AED groups, trends indicating likely relationship were observed.

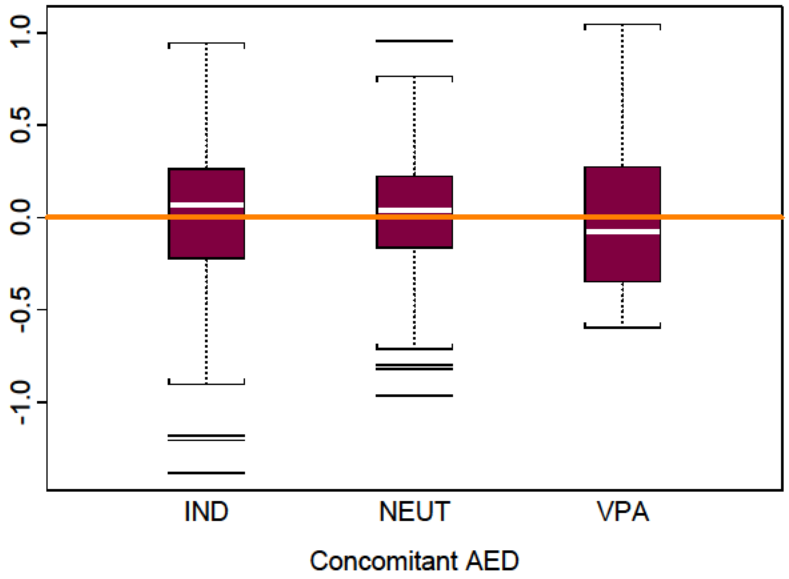
Figure 7: Concomitant AEDs (Inducers, VPA), body weight and post-natal age are the covariates likely to explain the between subject variability in oral clearance (CL/F) of lamotrigine. **(Note: This is not the final model).**





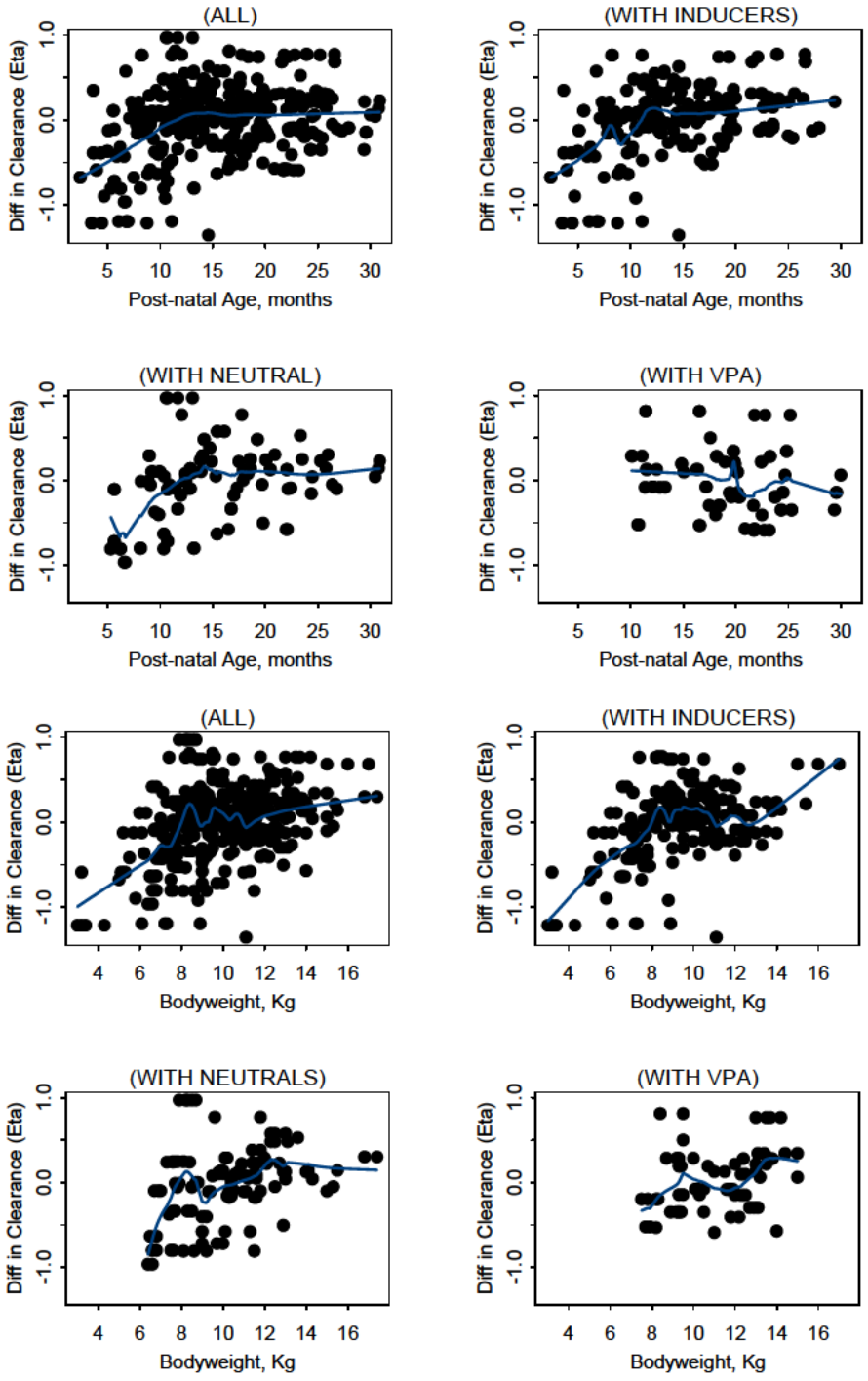
- None of the screened covariates showed any systematic relationship with V/F.
- Lamotrigine is predominantly cleared hepatically by glucuronidation. It has been known that VPA administration inhibits glucuronidation and other concomitant AEDs such as Phenytoin, Carbamazapine, etc induce glucuronidation. Adjustment of oral clearance to account for the effects of concomitant AEDs reduces the between patient variability from 74% to 48% (**Figure 8**).

Figure 8: Adjustment for the effect of concomitant AEDs reduces between subject variability from 74% to 48% **(Note: This is not the final model).**



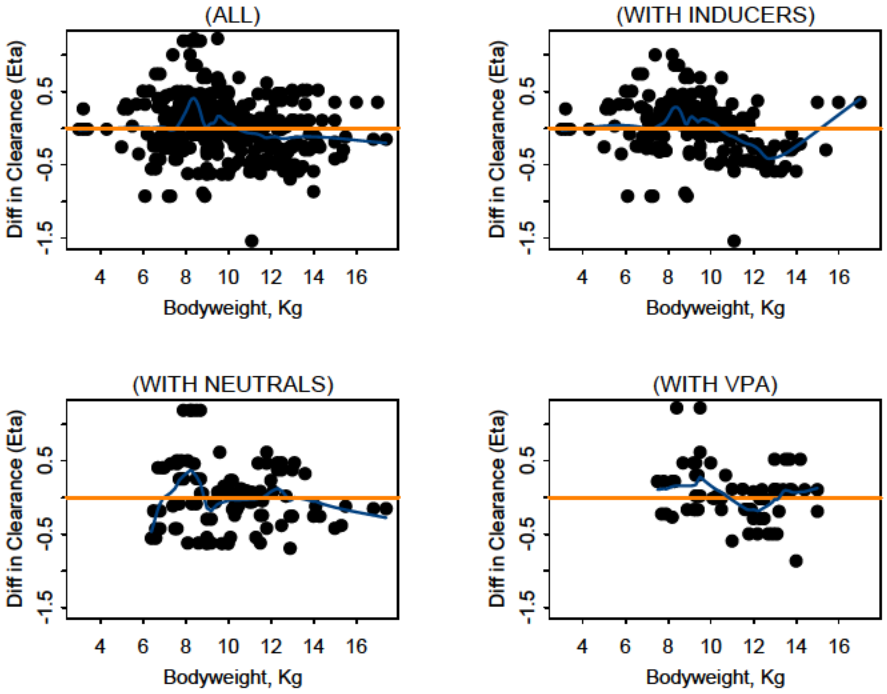
- Plots of difference in oral clearance from the mean adjusted for concomitant AEDs show a systematic trend with bodyweight and post-natal age (**Figure 9**). These covariates are like to further explain between subject variability associated with oral clearance of lamotrigine.

Figure 9: Post-natal age and body weight are likely covariates to further explain the between subject variability in CL/F. **(Note: This is not the final model).**



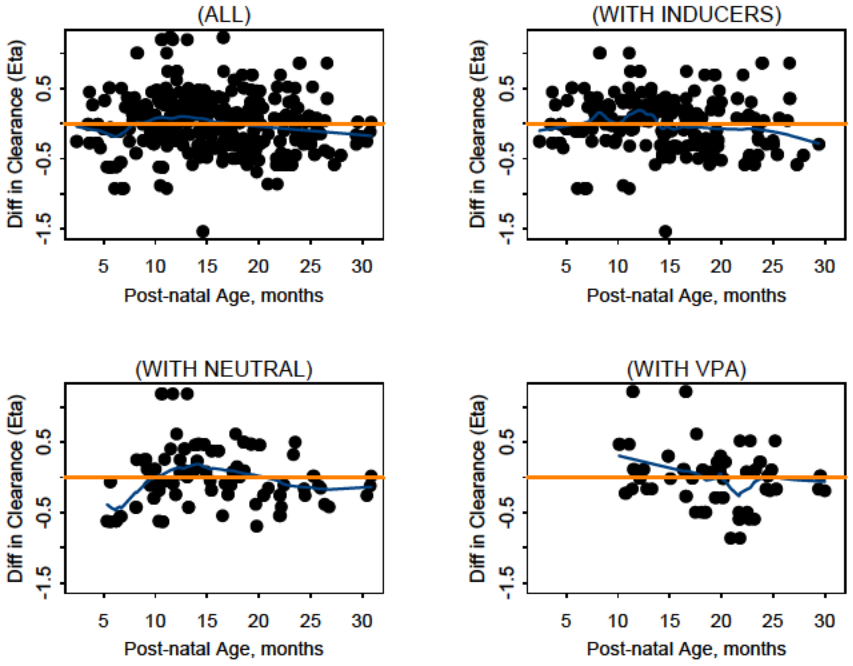
- Since post-natal age and body weight are highly correlated as shown in Figure 3, body weight was tested to explain further variability in the oral clearance of lamotrigine. Body weight decreased the variability in oral clearance of lamotrigine from 48% to 45%.

Figure 10: Body weight reduces the between patient variability of concomitant AEDs adjusted oral clearance from 48% to 45%. **(Note: Final Model)**



- Further, inclusion of body weight accounted for the age-related effects on oral clearance of lamotrigine as shown in Figure 11.

Figure 11: incorporation of body weight accounts for the age-related effects on the oral clearance of lamotrigine.



- The sequence of the model building is listed in **Table 9** below. Incorporation of the concomitant AEDs and body weight not only resulted in statistically significant drop in the objective function value, but also decrease the inter-individual variability from 73% to 45 %.

Table 9: Model building sequence

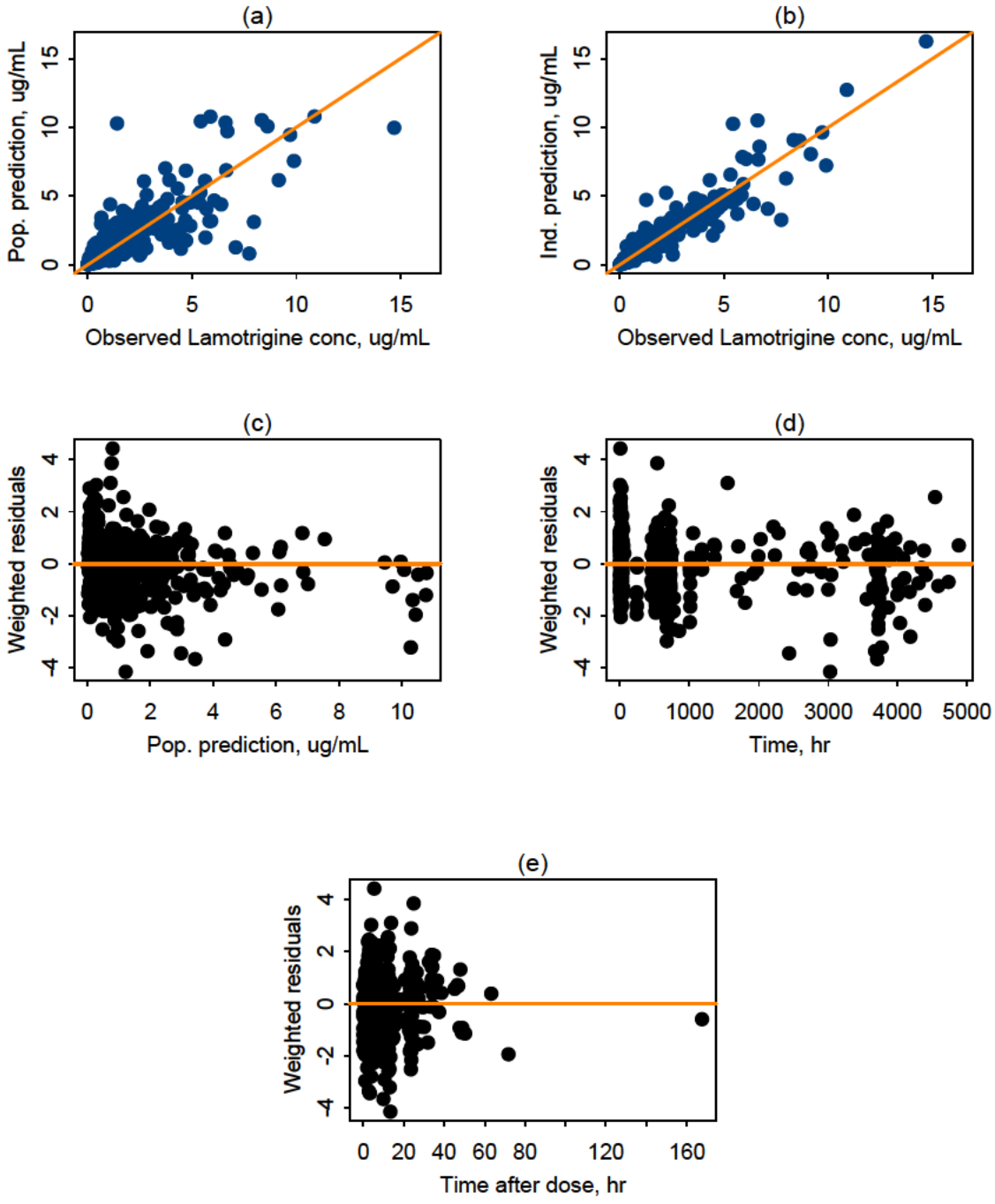
Model	Minimum Objective Function	Delta	dof	Significance
Base model	-225.4			
Adjusting for concomitant AEDs (Inducers and VPA)	-323.4	98	2	p<0.001
Adjusting for AEDs and WT	-397.3	73.9	3	p<0.001

- The pharmacokinetic parameters from the final model are shown in the Table below (**Table 10**). The diagnostic plots for the final model are shown in the figure below (**Figure 12**).

Table 10: Between patient variability in oral clearance of lamotrigine is explained by VPA, INDUCERS and bodyweight. **(Note: Final model).**

PK Parameter	Population Mean (%RSE)	Between-Subject Variability (%CV) (%RSE)
K_a (1 /hr)	2.1 (39)	N.E
CL/F (L/hr) ***Effect of VPA*** ***Effect of IND*** ***Effect of Body weight***	0.58 (8) -0.70 (6) 0.8 (22) 1.3 (15)	45 (21)
V/F (L)	35.9 (19)	73 (25)
Residual Error (%CV)	33 (14)	N.E

Figure 12: Model diagnostics:- The population model predicts the concentration reasonably well.



- The oral clearance of lamotrigine for the various concomitant AED groups with the final model is shown in the **Table 11** below.

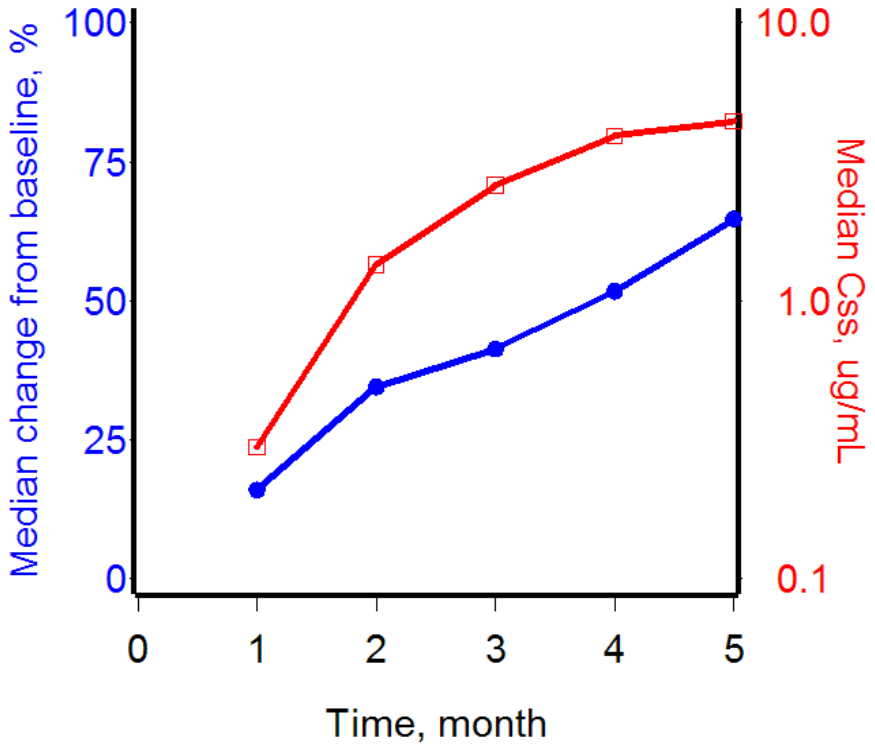
Table 11: Comparison of oral clearance of lamotrigine across different concomitant AED groups after accountng for body weight effects.

Concomitant AED	Oral Clearance (L/h)			
	Mean	Median	Min	Max
Inducer	1.03	0.98	0.23	2.68
Neutral	0.66	0.62	0.20	1.49
VPA	0.23	0.19	0.11	0.51

Exposure-Response

Exploratory graphical evaluation for the exposure and the percent change from baseline in partial seizures for 4-week increments during the open-label phase revealed that higher exposures resulted in greater reductions in seizure frequency as shown in **Figure 13** below. However, on should be cautious in attributing the reduction in seizure frequency to lamictal as it could be confounded with time. The data from the double-blind phase might be useful in teasing out the confounding effect of time as it has a placebo arm.

Figure 13: Increased exposure results in greater reduction in partial seizure frequency. (Note: Time could be confounding the effect of exposure).



Conclusion

- A one-compartment open model with 1st order absorption and elimination adequately describes the serum concentration time profile of lamotrigine in pediatric patients aged 2.4 – 25.8 months.
- Concomitant AEDs (Inducers and VPA) and body weight were found to be the major explanatory variables for the inter-individual variability associated with oral clearance of lamotrigine.
- The oral clearance of lamotrigine is increased by 80% when administered with glucuronidation inducing AEDs such as Phenytoin, Carbamazapine, Phenobarbital, etc.
- The oral clearance of lamotrigine is decreased by 70% when administered with VPA.
- Bodyweight accounts for the age-related effects on the oral clearance of lamotrigine.
- Increasing exposures in open label phase result in greater reduction of seizure frequency compared to historical baseline. However, time and drug effect are confounded in the present exploratory analysis.

3 Appendix 1

Please provide the datasets with the following variables necessary for exposure – response analysis:

1. Dosing History

VARIABLE	DESCRIPTION	TYPE
PPT	Unique Identifier of the subject	Numeric
STUDYID	Current Study; =20006 or 20007	Numeric
DOSE	Dose (mg/kg)	Numeric
ACTDOSTIM	Dosing Time	DATE7.
DOSTIM	Dosing Time (Nominal Time in days)	Numeric
AEDGRP	Concurrent AED category: 1-inducers, 2-Neutral, 3-VPA	Numeric
WEIGHT	Weight (kg) for each dose	Numeric
PHASE	Study Phase;0 – baseline, 1 – Open label, 2 – Double – blind, followup	Numeric
DRG	Treatment associated with drug interval; LTG – Lamictal, PBO – Placebo, OFF – Off drug, GAP – Gap in dosing	Character
RACE	Race; W – White, B – Black, A – Asian, H – Hispanic American, X - Other	Character
AGE	Age in months	Numeric
PTRT	Randomized Treatment in Study 20006; 1 – Placebo, 2 - Lamictal	Numeric
ESCAPE	Met Escape Criteria in Study 20006; 1 – Yes, 2 – No, 3 – Not Studied	Numeric
ESC_COMMENT	Reason for meeting Escape Criteria in Study 20006	Character

2. RESP1 (Seizure Counts by 4 week intervals)

VARIABLE	DESCRIPTION	TYPE
PPT	Unique Identifier of the subject	Numeric
STUDYID	Current Study; =20006 or 20007	Numeric
AVGDOS4	Average Daily Dose for the 4 – week interval (mg/kg/day)	Numeric
L28_DOS	Average daily dose for the last 28 days (mg/kg/day)	Numeric
LASTDOS	Final dose in the 4 – week interval (mg/kg/day)	Numeric
PHASE	Study Phase; 0 – baseline, 1 – Open label, 2 – Double – blind, 95 - followup	Numeric
PTRT	Randomized Treatment in Study 20006; 1 – Placebo, 2 - Lamictal	Numeric
WEEK4	4-week interval; 1=1-4 weeks 2=4-8 weeks 3=9-12 weeks 4=13-16 weeks 5=17-20 weeks 6=21-24 weeks 7=25-28 weeks 8=29-32 weeks 99=TERM (last 28 days of OLP) 100=4-8 weeks (or Entire DBP if subj. in DBP >8 wks)	Numeric
DAYS	Number of days in the 4-week interval	Numeric
WK4SUM	Total seizure frequency during the 4 – week interval	Numeric
SZTYPE	Seizure Type; A – Simple Partial B – Complex Partial C – Secondarily Genaralized T – A+B+C (Sum of A,B,C) D – Primary Genaralized	Numeric
AVGWK4	Average Weekly seizure frequency during the 4 – week interval	Numeric
L28_OLP	Total seizure frequency during the last 28 days of OLP	Numeric
AVGL28	Average weekly seizure frequency during the last 28 days	Numeric
HISTBSLN	Historical Baseline Partial Seizure Count	Numeric
BSLN4SUM	Total Seizure frequency during the 4-week interval of the historical baseline	Numeric
AVGBSLN	Average weekly baseline seizure count	Numeric
PCTCHG	Percent Change from Historical Baseline in	Numeric

	observed seizure frequency for 4 – week intervals	
PCTCHG_DBP	Percent Change from last 28 days of OLP in observed seizure frequency for 4 – week intervals	Numeric

3. RESP2 (Weekly Seizure frequency)

VARIABLE	DESCRIPTION	TYPE
PPT	Unique Identifier of the subject	Numeric
STUDYID	Current Study; =20006 or 20007	Numeric
WEEK	Week number within study phase	Numeric
RAWCNT	Total partial seizure count for study week	Numeric
SZTYPE	Seizure Type; A – Simple Partial B – Complex Partial C – Secondarily Genaralized T – A+B+C (Sum of A,B,C) D – Primary Genaralized	Numeric
WKDYS	No. of days contributing to total seizure count	Numeric
CNT	All Seizure frequency per week (RAWCNT/WKDYS)	
AVGWKDOS	Average Daily Dose per week (mg/kg/day) (Total Daily Dose for the week/WKDYS)	Numeric
WEIGHT	Weight (kg) for each dose	Numeric
PHASE	Study Phase; 0 – baseline, 1 – Open label, 2 – Double – blind, 95 – Follow up	Numeric
DRG	Treatment associated with drug interval; LTG – Lamictal, PBO – Placebo, OFF – Off drug, GAP – Gap in dosing	Character
RACE	Race; W – White, B – Black, A – Asian, H – Hispanic American, X - Other	Character
AGE	Age in months	Numeric
PTRT	Randomized Treatment in Study 20006; 1 – Placebo, 2 – Lamictal, 0 – Study 20007	Numeric

---

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

/s/

Sally Yasuda
5/23/2007 11:53:23 AM
BIOPHARMACEUTICS

Rajnikanth Madabushi
5/23/2007 12:01:05 PM
PHARMACOLOGIST

Yaning Wang
5/23/2007 11:25:21 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/24/2007 12:42:35 AM
BIOPHARMACEUTICS