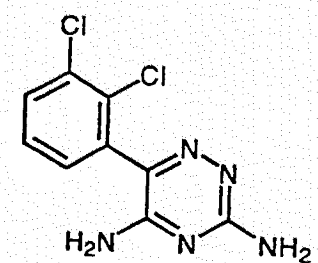
ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SUMMARY OF LAMOTRIGINE IN SUPPORT OF THE MONOTHERAPY FOR PARTIAL SEIZURES IN ADULT PATIENTS

1. INTRODUCTION

LAMICTAL† (lamotrigine), an antiepileptic compound of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs (AEDs). Its chemical name is 6–(2,3–dichlorophenyl)–1,2,4–triazine–3,5–diamine, its molecular formula is $C_9H_7N_5CL_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream–colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25 degrees C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25 degrees C). The structure formula is:



LAMICTAL is approved in the US as add–on therapy in the treatment of partial seizures in patients over 16 years of age (the original NDA 20–241 was submitted 31 December 1991). Currently, LAMICTAL is supplied for oral administration as 25 mg, 100 mg, 150 mg, and 200 mg tablets. In this supplemental NDA (sNDA), Glaxo Wellcome Inc. is requesting approval for monotherapy for partial seizures in patients over 13 years of age. Efficacy and safety data obtained in the pivotal trial US 30/31 in support of the current application are included in Item 8, Clinical Data Section. In this section, the clinical pharmacokinetics of lamotrigine in adults are reviewed, pharmacokinetics of lamotrigine in patients between 13 and 18 years of age are described and the pharmacokinetic analysis of lamotrigine performed in study US 30/31 is presented. Details about study US 30/31 can be found in the NDA Summary (Volume 1) and the final study report in Item 8, Section 8.4 of this sNDA.

2. CLINICAL PHARMACOKINETICS OF LAMOTRIGINE IN ADULTS

The pharmacokinetics of lamotrigine have been studied in patients with epileptic seizures, young and elderly healthy volunteers, and volunteers with

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chronic renal failure. The following is a summary of pharmacokinetic related information in the current US Package Insert for LAMICTAL Tablets. These data were included in the original submission of NDA 20–241 (LAMICTAL Tablets; submitted 31 December 1991).

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first–pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur from hours in healthy volunteers or patients with epilepsy following single or multiple dose administration.

Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 µg/mL. Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproic acid. Lamotrigine at therapeutic concentrations did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2–N–glucuronide conjugate. After oral administration of 240 mg lamotrigine to six healthy volunteers, 94% of the administered dose was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2–N–glucuronide (76%), a 5–N–glucuronide (10%), a 2–N–methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Estimates of mean apparent plasma clearance (CL/F) and plasma half–life ($t_{1/2}$) in epileptic patients taking hepatic enzyme–inducing antiepileptic drugs (EIAEDs, including carbamazepine, phenytoin, phenobarbital and primidone), enzyme inhibitor valproate or both were 1.10, 0.28 or 0.53 mL/min/kg and 14.4, 58.8 or 27.2 hours, respectively. Therefore the elimination of lamotrigine in epileptic patients is dependent on the concomitant medication.

Following multiple doses (150 mg b.i.d.) to normal volunteers taking no other medications, lamotrigine induced its own metabolism resulting in a 25% decrease in $t_{1/2}$ and a 37% increase in CL/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self induction by LAMICTAL dose not occur when LAMICTAL is given as add–on therapy in patients receiving EIAEDs.

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In two small studies (n = 7 and 8) of patients with epilepsy who were maintained on other antiepileptic drugs there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 mg to 350 mg b.i.d.

Twelve volunteers with chronic renal failure (mean creatinine clearance = 13 mL/min; range and another six individuals undergoing hemodialysis were each given a single 100 mg dose of LAMICTAL. The mean plasma half–lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20 (% of the amount of lamotrigine present in the body was eliminated during a 4–hour hemodialysis session.

In a single dose study (150 mg LAMICTAL), the pharmacokinetics of lamotrigine in twelve elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min; range were similar to those of young healthy volunteers in other studies. The clearance of lamotrigine is not affected by gender. The apparent oral clearance of lamotrigine was 25% lower in noncaucasians than Caucasians.

The interaction of lamotrigine with phenytoin, carbamazepine, and valproic acid has been studied. LAMICTAL has no appreciable effect on steady–state phenytoin and carbamazepine plasma concentration. When LAMICTAL was administered to 18 healthy volunteers receiving valproic acid (VPA), the trough steady–state VPA concentrations in plasma decreased by an average of 25% over a 3–week period, and then stabilized.

Lamotrigine is an inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications which inhibit folate metabolism.

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3. PHARMACOKINETICS OF LAMOTRIGINE IN PATIENTS BETWEEN 13 AND 18 YEARS OF AGE

The pharmacokinetics of lamotrigine in adults are summarized in the previous section. A population pharmacokinetic analysis in pediatric patients with epilepsy receiving concomitant AEDs has been performed using the nonlinear mixed effect modeling (NONMEM) approach (Appendix A). The analysis included 652 steady–state plasma concentrations from 204 patients, among which 23 were in the age range of 13 to 18 years, enrolled in three lamotrigine add–on efficacy and safety trials The estimated typical values of apparent clearance in patients at various ages receiving different concomitant AEDs are summarized in the following table.

Concomitant AED	Apparent Clearance (mL/min/kg)		
	1.5 to < 6 years	6 to < 13 years	13 to 18 years
EIAEDs	2.3 (n = 27)	1.6 (n = 63)	1.3 (n = 11)
EIAEDs + VPA	0.9 (n = 5)	0.6 (n = 32)	0.5 (n = 8)
VPA	0.5 (n = 19)	0.3 (n = 35)	0.3 (n = 4)

Apparent clearance in patients 13 to 18 years old receiving both EIAEDs and VPA was estimated as 0.5 mL/min/kg. Mean apparent clearance of lamotrigine in adult patients taking both EIAEDs and VPA and that in adults taking lamotrigine alone are 0.53 mL/min/kg (range and 0.58 mL/min/kg (range , respectively (current US Package Insert). Apparent clearance of lamotrigine in patients between 13 and 18 years of age taking both EIAEDs and VPA (0.5 mL/min/kg) is similar to that in adults taking the same types of concomitant AEDs (0.53 mL/min/kg). It is not unreasonable to project that the clearance in patients 13 to 18 years old receiving lamotrigine alone is similar to that in adults receiving no concomitant AEDs (0.58 mL/min/kg). Therefore the apparent clearance of LTG in the absence of other AEDs in patients between 13 and 18 years of age is predicted to be approximately 0.58 mL/min/kg.

4. PHARMACOKINETIC ANALYSIS OF LAMOTRIGINE IN STUDY US 30/31

4.1 Background

The primary objective of study US 30/31 (A Multicenter, Double–Blind, Active–Control Evaluation Of The Efficacy And Safety Of Lamotrigine Monotherapy In Patients With Partial Seizures) was to compare the efficacy and safety of lamotrigine (LTG) monotherapy (500 mg/day) to valproate (VPA) monotherapy (1000 mg/day) in adult (age 13 to 73 years) outpatients with partial seizures, with or without secondarily generalized tonic–clonic seizures. Efficacy was based on the proportion of patients who discontinued treatment due to meeting one of the "escape" criteria (defined below). One of the secondary objectives of the study was to obtain LTG pharmacokinetic data during add–on treatment, during the withdrawal of concomitant liver enzyme–inducing antiepileptic drugs (EIAEDs) carbamazepine (CBZ) and phenytoin (PHT), and during LTG monotherapy.

Following screening, eligible patients entered an 8–week Baseline Phase (weeks 1 through 8) during which patients received CBZ or PHT and baseline data on seizure frequency and safety parameters were obtained. Patients then entered an 8–week Treatment Transition Phase (weeks 9 through 16) during which the study medication (either LTG and corresponding VPA placebo or VPA and corresponding LTG placebo) was gradually added to the concomitant AED over the initial four weeks and the concomitant AED was then tapered–off over the remaining four weeks. Patients who had fully converted to monotherapy continued to receive treatment for 12 additional weeks (Monotherapy Phase, weeks 17 through 28) unless they met one of the criteria for escape (defined below) or they reported an adverse experience requiring discontinuation from the study. Patients entered the Follow–up Phase (weeks 29 through 31) following completion of the Monotherapy Phase or once conditions were met for premature discontinuation. Study medication was tapered off under double–blind conditions; treatment with concomitant AED was initiated at the same time.

Escape criteria for each patient were determined upon completion of Baseline and included evaluation of simple partial, complex partial, and secondarily generalized seizures. Patients discontinued study treatment when one of the following escape criteria were met: (1) doubling of the average monthly seizure count, (2) doubling of the highest consecutive 2–day seizure frequency, (3) emergence of a new seizure type that was more severe than the current seizure type(s), or (4) clinically significant prolongation of generalized tonic–clonic seizures. If a patient met one of the escape criteria, the dosage of the concomitant AED can be adjusted or a new AED can be added at the investigator's discretion.

A total of 156 patients, 91 females and 65 males ages 13 to 73 years, were randomized to receive LTG (n=76) or VPA (n=80). Of these, 114 patients completed the study (28 completed LTG monotherapy treatment, and 22 escaped in the LTG group; 13 completed VPA monotherapy treatment, and 51 escaped in the VPA group). A total of 26 patients in the LTG group and 16 patients in the VPA group were withdrawn during their participation in the study. Twenty (20) of these patients (14 in the LTG group and 6 in the VPA group) withdrew due to adverse experiences

4.2 Objectives

The objectives of the pharmacokinetic analysis in study US 30/31 were 1) to compare mean plasma concentrations of lamotrigine and concomitant AEDs between patients who escaped and those who remained in the study at protocol specified evaluation times; and 2) to assess the time required for plasma concentration of lamotrigine to reach a new steady–state following withdrawal of CBZ and PHT.

4.3 Methodology

Blood samples were collected at the end of weeks 8, 10, 12, 14, 16, 20, 24 and 28 to determine plasma concentrations of LTG and VPA and at end of weeks 0, 4, 8, 10, 12, 14 and 16 to determine plasma concentrations of CBZ and PHT. All samples were collected immediately prior to the next dose of medication in order to obtain trough plasma concentrations, except for week 20, 24 and 28 samples which were collected randomly throughout the dosing interval.

Plasma concentrations of lamotrigine at baseline and at the end of study weeks 10, 12, 14, and 16 (Treatment Transition) and at end of study weeks 20, 24 and 28 (Monotherapy Period) were summarized by concomitant AED (CBZ or PHT). Trough plasma concentrations of CBZ and PHT at baseline and at end of study weeks 10, 12, 14, and 16 were also summarized. For patients meeting escape criteria, plasma concentrations of lamotrigine, CBZ, and PHT recorded after their date of escape were excluded from the analysis. The concentrations of lamotrigine, CBZ, and PHT were compared between the completers and the escapers. At each assessed time point, the completer group included those who remained in the study until at least the next sampling time, and the escaper group included those who escaped between the current sampling point and the next sampling point.

Changes in lamotrigine concentrations from the end of study week 20 to the end of study weeks 24 and 28 (during the Monotherapy Period) were calculated and 95% confidence intervals were constructed. For patients meeting escape criteria, lamotrigine levels obtained after the recorded date of escape were excluded from the calculation. To ensure appropriate comparison of lamotrigine concentrations between study week 20 and study week 24 or 28, the elapsed time from dosing to sampling at these occasions were examined.

4.4 Results

Table 1 summarizes the plasma concentration of study drugs LTG and VPA during various phases of the study. Mean plasma concentrations of concomitant AEDs by visit are presented in Table 2. Plasma concentrations of study drugs and those of concomitant AEDs in completers versus escapers are presented in Table 3 and Table 4. Plasma concentration of study drugs during the Monotherapy Period of the study are summarized in Table 5 and the change in study drug concentrations at weeks 24 and 28 from week 20 are shown in Table 6. The mean elapsed time from dosing to sampling at various sampling events during monotherapy phase is compared in Table 7.

Lamotrigine concentrations were not consistently different between the completers and the escapers in patients receiving CBZ or in patients receiving PHT (Table 3). Similarly, no consistent differences in trough concentrations of CBZ or PHT were detected between the completers and the escapers (Table 4).

Mean plasma concentrations of lamotrigine increased from baseline through study week 12 during lamotrigine dose escalation (Table 1). Concentrations of lamotrigine continued to increase through study week 16 during the gradual reduction in dosage of concomitant EIAEDs. The new steady–state of lamotrigine did not appear to be reached until study week 24, 12 weeks after the dose reduction of CBZ and PHT was started and 8 weeks after the concomitant AEDs were completely withdrawn (Table 1). In the CBZ group, the median increase in lamotrigine concentration was 1.4 μg/mL or 19% from study week 20 to week 24. The concentrations did not further increase from week 24 to week 28. The corresponding changes in the PHT group could not be precisely estimated due to the small sample size (Table 6). However, lamotrigine concentrations were slightly higher in patients who had received

CBZ compared to those who had received PHT (Table 5). The mean elapsed time from dosing to sampling was similar among study weeks 20, 24 and 28 (Table 7).

The mean trough plasma concentrations of CBZ and PHT did not change appreciably until after study week 12 when the reduction of the daily dosage of these concomitant AEDs was started (Table 2).

4.5 Discussion

In general, mean plasma concentrations of lamotrigine were comparable between the completers and the escapers at protocol specified sampling times. Similarly, no consistent differences in trough concentrations of CBZ or PHT were detected between the completers and the escapers. Therefore, patient escape from the study did not appear to be caused by lower plasma concentrations of lamotrigine and concomitant AED (CBZ or PHT).

The mean trough plasma concentrations of CBZ and PHT did not change appreciably until after study week 12 when the reduction of the daily dosage of these concomitant AEDs was initiated, indicating that the pharmacokinetics of CBZ and PHT were not affected by dose escalation of lamotrigine during the first 4 weeks of Treatment Transition.

4.6 Conclusions

Plasma concentrations of lamotrigine and concomitant AEDs carbamazepine and phenytoin were comparable between patients escaped from the study and those remained in the study. Plasma concentration of lamotrigine appeared to reach a new steady–state between 4 and 8 weeks after complete withdrawal of carbamazepine.

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5. OVERALL CONCLUSIONS

1. The pharmacokinetics information of lamotrigine in adult subjects receiving no concomitant medication is provided in the current US Package Insert for LAMICTAL Tablets;

2. The apparent clearance of lamotrigine in the absence of other AEDs in patients between 13 and 18 years of age is expected to be similar to that in adults (0.58 mL/min/kg);

3. When patients were switched from carbamazepine monotherapy to lamotrigine monotherapy, plasma concentration of lamotrigine appeared to reach a new steady–state between 4 and 8 weeks after complete withdrawal of carbamazepine.

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Table 1
Summary of Study Drug Plasma Concentrations by Visit

		LAMICTAL						VPA					
		Plasma Concentration (ug/mL)						Plasma Concentration (ug/mL)					
Phase	Study Week	N	Mean	SD	Median	Min.	Max.	N	Mean	SD	Median	Min.	Max.
B/Wk8	8	62	0.0	0.0	0.0			61	0.7	4.0	0.0		
T/Wk2	10	58	2.6	1.3	2.5			64	46.9	21.6	45.4		
T/Wk4	12	54	4.0	2.3	3.7			67	46.5	19.7	45.1		
T/Wk6	14	49	4.9	2.9	4.2			54	43.4	19.0	42.5		
T/Wk8	16	30	5.7	2.8	5.2			38	44.4	18.9	45.5		
M/Wk4	20	31	7.9	3.7	7.3			18	67.4	20.3	70.8		
M/Wk8	24	28	10.1	5.5	8.9			13	68.7	18.2	71.9		
M/Wk12	28	16	8.7	3.8	7.9			9	72.3	23.5	67.9		

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up. Post '/' indicates specific timepoint within phase.

Table 2
Summary of Concomitant AED Plasma Concentrations by Visit

AED	Phase	Study Week	LAMICTAL GROUP Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.	VPA GROUP Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.
CBZ	B/Wk0	0	47	9.5	2.7	8.7			46	9.2	2.1	9.2		
	B/Wk4	4	33	9.5	2.5	9.0			30	9.9	2.4	9.7		
	B/Wk8	8	45	9.1	2.7	8.4			45	9.4	2.8	9.3		
	T/Wk2	10	40	8.5	3.2	8.6			42	8.5	2.8	8.1		
	T/Wk4	12	34	7.9	2.9	7.4			41	8.2	2.2	8.5		
	T/Wk6	14	31	5.6	2.0	5.7			35	7.0	2.2	6.8		
	T/Wk8	16	24	3.1	1.7	3.0			23	3.6	2.2	3.2		
PHT	B/Wk0	0	28	17.8	6.7	18.0			34	19.9	9.5	18.0		
	B/Wk4	4	22	19.6	9.3	18.5			25	19.0	7.8	18.0		
	B/Wk8	8	27	19.4	7.4	19.0			33	18.5	8.4	17.0		
	T/Wk2	10	27	20.3	8.6	18.0			29	14.9	7.2	14.0		
	T/Wk4	12	21	18.1	6.9	17.0			29	13.9	7.8	14.0		
	T/Wk6	14	19	8.9	4.8	8.0			22	6.8	5.0	5.0		
	T/Wk8	16	10	3.4	2.6	1.5			14	2.4	2.3	1.5		

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

Table 3
Summary of Study Drug Plasma Concentrations by Strata Analysis

Phase	Study Week	Efficacy	Baseline AED	LAMICTAL Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.	VPA Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.
B/Wk8	8	Completer	All	42	0.0	0.0	0.0			47	0.4	2.8	0.0		
			CBZ	25	0.0	0.0	0.0			29	0.0	0.0	0.0		
			PHT	17	0.0	0.0	0.0			18	1.1	4.5	0.0		
T/Wk2	10	Completer	All	40	2.5	1.4	2.1			49	47.1	23.0	45.2		
			CBZ	23	2.7	1.4	2.7			33	49.7	24.7	45.5		
			PHT	17	2.3	1.4	1.7			16	41.8	18.5	38.6		
T/Wk4	12	Completer	All	38	3.9	2.2	3.5			51	49.6	20.3	46.2		
			CBZ	24	4.4	2.3	4.4			34	51.1	19.5	46.0		
			PHT	14	3.0	1.8	2.6			17	46.5	22.0	52.9		
		Escaper	All	6	4.9	3.3	3.7			7	28.3	6.5	29.6		
			CBZ	2	3.7	0.0	3.7			3	28.5	6.6	26.0		
			PHT	4	5.6	4.0	3.9			4	28.2	7.5	30.7		
T/Wk6	14	Completer	All	34	4.6	2.7	4.0			32	43.2	21.6	42.5		
			CBZ	23	5.3	3.0	4.6			22	46.7	22.3	47.5		
			PHT	11	3.1	1.1	3.0			10	35.5	18.5	32.6		
		Escaper	All	8	4.4	2.4	3.7			15	42.3	14.9	36.2		
			CBZ	3	7.1	0.2	7.0			9	43.9	16.3	35.6		
			PHT	5	2.7	1.2	3.1			6	40.0	13.6	40.3		
T/Wk8	16	Completer	All	25	5.6	2.9	4.9			21	49.1	16.8	49.1		
			CBZ	18	6.4	2.8	6.1			15	54.2	15.8	52.4		
			PHT	7	3.5	1.9	3.3			6	36.1	12.2	35.9		
		Escaper	All	2	4.3	1.9	4.3			11	40.9	19.8	42.4		
			CBZ	1	2.9		2.9			6	38.4	26.5	37.8		
			PHT	1	5.6		5.6			5	44.0	9.1	42.4		
M/Wk4	20	Completer	All	28	7.8	3.0	7.2			10	70.6	20.9	75.1		
			CBZ	21	8.1	3.1	7.3			6	72.9	20.8	75.1		
			PHT	7	7.0	2.9	7.2			4	67.1	23.7	64.6		
		Escaper	All	0						6	64.0	23.3	63.7		

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up. Post '/' indicates specific timepoint within phase.

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Table 3
Summary of Study Drug Plasma Concentrations by Strata Analysis

Phase	Study Week	Efficacy	Baseline AED	LAMICTAL Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.	VPA Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.
M/Wk4	20	Escaper	CBZ	0						6	64.0	23.3	63.7		
M/Wk8	24	Completer	All	26	9.5	4.6	8.5			12	68.4	19.0	67.7		
			CBZ	20	10.3	4.8	9.5			8	66.8	22.6	61.1		
			PHT	6	6.8	3.0	6.5			4	71.5	10.3	74.1		
		Escaper	All	1	10.1		10.1			0					
			CBZ	1	10.1		10.1			0					
M/Wk12	28	Completer	All	15	8.8	3.9	7.9			9	72.3	23.5	67.9		
			CBZ	11	9.8	3.7	9.8			5	78.0	20.1	67.9		
			PHT	4	6.1	3.2	6.0			4	65.2	28.6	69.4		
		Escaper	All	1	6.5		6.5			0					
			CBZ	1	6.5		6.5			0					

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up. Post '/' indicates specific timepoint within phase.

Table 4
Summary of Concomitant AED Plasma Concentrations by Visit and Efficacy Response

AED	Phase	Study Week	Efficacy	LAMICTAL GROUP AED Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.	VPA GROUP AED Plasma Concentration (ug/mL) N	Mean	SD	Median	Min.	Max.
CBZ	B/Wk0	0	ALL	30	9.1	2.8	8.6			39	9.1	2.2	9.1		
			Completer	30	9.1	2.8	8.6			39	9.1	2.2	9.1		
	B/Wk4	4	ALL	23	9.6	2.6	9.0			25	9.8	2.5	9.6		
			Completer	23	9.6	2.6	9.0			25	9.8	2.5	9.6		
	B/Wk8	8	ALL	29	8.9	3.0	7.9			38	9.1	2.6	9.3		
			Completer	29	8.9	3.0	7.9			38	9.1	2.6	9.3		
	T/Wk2	10	ALL	29	8.2	3.3	8.0			35	8.4	2.9	8.0		
			Completer	29	8.2	3.3	8.0			35	8.4	2.9	8.0		
	T/Wk4	12	ALL	28	7.9	3.0	7.4			37	8.2	2.2	8.5		
			Completer	26	7.7	2.8	7.4			34	8.2	2.3	8.6		
			Escaper	2	10.6	6.6	10.6			3	8.5	2.2	8.0		
	T/Wk6	14	ALL	27	5.7	1.9	5.9			31	7.1	2.2	7.1		
			Completer	23	5.8	1.8	6.0			20	6.9	2.3	7.2		
			Escaper	4	5.4	2.4	4.8			11	7.3	2.2	6.8		
	T/Wk8	16	ALL	22	3.0	1.8	3.0			20	3.3	2.2	3.1		
			Completer	21	3.1	1.8	3.3			14	3.5	2.5	3.0		
			Escaper	1	1.0		1.0			6	2.9	1.1	3.1		
PHT	B/Wk0	0	ALL	20	17.4	7.0	17.0			25	19.6	8.7	17.0		
			Completer	20	17.4	7.0	17.0			25	19.6	8.7	17.0		
	B/Wk4	4	ALL	17	19.4	9.4	19.0			19	19.3	7.7	18.0		
			Completer	17	19.4	9.4	19.0			19	19.3	7.7	18.0		
	B/Wk8	8	ALL	19	19.3	7.2	18.0			24	18.4	8.9	17.0		
			Completer	19	19.3	7.2	18.0			24	18.4	8.9	17.0		
	T/Wk2	10	ALL	19	21.2	8.7	20.0			21	14.5	7.7	14.0		
			Completer	19	21.2	8.7	20.0			21	14.5	7.7	14.0		
	T/Wk4	12	ALL	19	18.5	7.2	18.0			23	13.7	7.8	13.0		
			Completer	15	18.3	6.4	18.0			20	13.0	7.3	13.5		
			Escaper	4	19.0	10.7	20.0			3	18.0	11.3	12.0		
	T/Wk6	14	ALL	16	8.8	5.2	8.5			19	6.4	4.8	5.0		

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

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Table 4
Summary of Concomitant AED Plasma Concentrations by Visit and Efficacy Response

				LAMICTAL GROUP AED Plasma Concentration (ug/mL)						VPA GROUP AED Plasma Concentration (ug/mL)					
AED	Phase	Study Week	Efficacy	N	Mean	SD	Median	Min.	Max.	N	Mean	SD	Median	Min.	Max.
PHT	T/Wk6	14	Completer	11	8.4	6.0	8.0			12	6.4	5.4	4.0		
			Escaper	5	9.6	3.2	10.0			7	6.4	3.9	5.0		
	T/Wk8	16	ALL	8	2.5	2.0	1.5			11	1.8	0.6	1.5		
			Completer	7	2.6	2.1	1.5			6	1.8	0.6	1.5		
			Escaper	1	1.5		1.5			5	1.8	0.7	1.5		

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

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Table 5
Plasma Concentration of Study Drug During Monotherapy Period

			LAMICTAL						VPA					
				Plasma Concentration (ug/mL)						Plasma Concentration (ug/mL)				
AED	Phase	Study Week	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
All	M/Wk4	20	31	7.9	3.7	7.3			18	67.4	20.3	70.8		
	M/Wk8	24	28	10.1	5.5	8.9			13	68.7	18.2	71.9		
	M/Wk12	28	16	8.7	3.8	7.9			9	72.3	23.5	67.9		
CBZ	M/Wk4	20	23	8.2	4.0	7.3			12	68.4	21.6	72.1		
	M/Wk8	24	22	11.1	5.7	9.9			8	66.8	22.6	61.1		
	M/Wk12	28	12	9.5	3.7	8.9			5	78.0	20.1	67.9		
PHT	M/Wk4	20	8	7.1	2.7	7.4			6	65.3	19.3	61.8		
	M/Wk8	24	6	6.8	3.0	6.5			5	71.6	8.9	73.1		
	M/Wk12	28	4	6.1	3.2	6.0			4	65.2	28.6	69.4		

PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase.

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Table 6
Change in Study Drug Concentration at Weeks 24 and 28 from Week 20

			LAMICTAL					VPA				
			Change in Study Drug Plasma Concentration from Week 20					Change in Study Drug Plasma Concentration from Week 20				
				Percent Change (%)		Absolute Change (ug/ml)			Percent Change (%)		Absolute Change (ug/ml)	
AED	Phase	Study Week	N	Median	95% CI	Median	95% CI	N	Median	95% CI	Median	95% CI
ALL	M/Wk8	24	27	10.5	(2.7,33.1)*	1.0	(0.2,2.4)*	11	9.8	(-10.1,24.8)	3.8	(-9.1,14.1)
	M/Wk12	28	15	9.2	(-9.8,28.6)	0.7	(-0.8,1.8)	9	0.7	(-17.7,10.9)	0.5	(-12.0,8.5)
CBZ	M/Wk8	24	21	19.0	(7.3,36.4)*	1.4	(0.6,3.0)*	6	3.0	(-21.8,18.1)	-0.1	(-15.2,14.1)
	M/Wk12	28	12	9.1	(-7.1,24.9)	0.5	(-1.0,2.3)	5	0.7	(-21.2,21.0)	0.5	(-16.4,16.4)
PHT	M/Wk8	24	6	-7.2	(-49.6,256.3)	-0.6	(-3.6,4.5)	5	24.8	(-13.6,50.4)	11.3	(-12.7,24.5)
	M/Wk12	28	3	9.2	(-56.3,135.6)	0.7	(-3.7,2.4)	4	0.2	(-32.2,13.3)	-1.8	(-14.7,10.7)

Analysis is restricted to observations with corresponding Week 20 value.
PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase.
'*' indicates significance of p <= 0.05.

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Table 7
Summary of Time after Last Dose to PK Sample

Phase	Study Week	LAMICTAL N	LAMICTAL Time from Last Dose to PK Sample (h) Mean	SD	Median	Min	Max	VPA N	VPA Time from Last Dose to PK Sample (h) Mean	SD	Median	Min	Max
M/Wk4	20	31	8.1	6.2	5.8			18	7.0	5.3	4.6		
M/Wk8	24	27	7.2	5.2	5.3			13	7.4	7.4	5.0		
M/Wk12	28	16	6.5	3.9	5.1			9	6.0	5.1	5.0		

PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase.