CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-764/S-011

20-241/S-017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
sNDA Filing Memo

NDA Numbers	20-241 S-017 20-764 S-011	**Brand Name**	Lamictal®
Related IND(s)	—	**Generic Name**	Lamotrigine
Related NDA(s)	None	**Pharmacologic Class**	Anticonvulsant
OCPB Division (I, II, III)	I HFD-860	**Chemical Class**	—
Medical Division	Neuropharmacology HFD-120	**Indication(s)**	Delay of depressive episodes in subjects with bipolar I disorder
OCPB Reviewer	***To-Be-Determined***	**Dosage Form**	Oral (IR) Tablets Oral Chewable Tablets
OCPB Team Leader	***To-Be-Determined***	**Strengths**	25, 100, 150, 200 mg IR tabs 2, 5, 25 mg Chew Tabs
Date of Submission	June 5, 2002		
Filing Meeting	July 2, 2002	**Route of Administration**	PO
PDUFA Due Date	April 6, 2003	**Sponsor**	GlaxoSmithKline
Division Due Date	March 6, 2003	**Priority Classification**	1S

1 BACKGROUND:

With the current application, GlaxoSmithKline, Inc. is seeking approval of the use of lamotrigine, LAMICTAL®, for the delay of depressive episodes in subjects with bipolar I disorder, as it is defined in DSM-IV.

LAMICTAL® is currently indicated as adjunctive therapy in adults with partial seizures; and in pediatric and adult patients for adjunctive therapy of the generalized seizures of Lennox-Gastaut syndrome. LAMICTAL® is also indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single EIAED.

Table 1 Associated NDAs

NDA	Formulation	Strengths	Approval Date
20-241	Oral Tablets	25 mg, 100mg, 150 mg, 200 mg	27 December, 1994
20-764	Chewable Oral Tablet	2 mg, 5 mg, 25 mg	24 August 1998

The proposed mechanism of action of LAMICTAL involves an effect on sodium channels. *In vitro* pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

2 SUBMITTED STUDIES:

The HPBIO section of the sNDA provides a summary of two clinical pharmacology studies including pharmacokinetic aspects conducted in healthy volunteers to support the lack of interaction when co-administering bupropion or lithium with lamotrigine (section 6.2.1, 6.2.2).

Also provided in the clinical safety and efficacy section are pharmacokinetic endpoints conducted in clinical patient studies. These data appear to evaluate the association of lamotrigine concentrations with efficacy and safety (i.e. withdrawals).

Two new *in vitro* studies have been carried out with lamotrigine. The first has assessed the inhibition of lamotrigine glucuronidation by selected drugs, using suspended human hepatocytes. The second has assessed the inhibitory effect of lamotrigine on CYP2D6 enzyme activity in human liver microsomes, and are located in the pharmacology / toxicology section.

All clinical studies were conducted with the currently marketed formulations, thus no new CMC or other dissolution data is provided.

3 ABILITY TO LOCATE INFORMATION AND LEGIBILITY:

All information was locatable and legible.

The entire application is provided in electronic format and is available at:
\\cdsesub1\N20241\S_017\2002-06-05
\\cdsesub1\N20764\S_011\2002-06-05

Not all information is located in HPBIO section. However, it can be found in other sections and is available to the reviewer electronically.

4 DATA FORMAT:

Pharmacokinetic data for clinical efficacy and safety studies were not provided in SAS transport file format. However, they were in non-image pdf format. This allows the information to be copied into data analysis programs for analysis.

Summary data analyses were lacking in detail, (e.g. only geometric mean and median) and the data will need to be reanalyzed. However, due to the electronic format and how the data was provided this should be easier than usual.

5 BIOANALYTIC DATA:

Bioanalytic data (method validation etc.) are provided in each study report. However this reviewer did not find summary tables.

6 CONCLUSION:

File-able

7 REQUESTS FOR INFORMATION:

The sponsor is requested to provide raw data for studies in the HPBIO section in SAS transport file format.

8 SIGNATURES:

Primary Reviewer for Filing: **Signature and Date**	**Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.**	**July 22, 2002**
Team Leader for Filing: **Signature and Date**	**Raman Baweja, B.S. Pharm., Ph.D.**	**July 22, 2002**

CC: **NDA 20-241** **S-017**
NDA 20-764 **S-011**
HFD-860 (KavanaghR, BawejaR, MehtaM, MarroumP)
HFD-120 (WareJ)
CDR (Barbara Murphy)

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/s/

Ron Kavanagh
7/22/02 02:11:13 PM
BIOPHARMACEUTICS

Raman Baweja
7/22/02 06:02:29 PM
BIOPHARMACEUTICS
Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-241 S-017 20-764 S-011	**Brand Name**	Lamictal®
OCPB Division (I, II, III)	I	**Generic Name**	Lamotrigine
Medical Division	Neuropharmacology HFD-120	**Drug Class**	Anticonvulsant
OCPB Reviewer	*To-Be-Determined*	**Indication(s)**	Delay of depressive episodes in subjects with bipolar I disorder
OCPB Team Leader	*To-Be-Determined*	**Dosage Form**	Oral (IR) Tablets Oral Chewable Tablets
Date of Submission	June 5, 2002	**Dosing Regimen**	
Filing Meeting	July 2, 2002	**Route of Administration**	PO
Estimated Due Date of OCPB Review	February 20, 2003	**Sponsor**	GlaxoSmithKline
PDUFA Due Date	April 6, 2003	**Priority Classification**	1S
Division Due Date	March 6, 2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	2		
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?	X	
QBR questions (key issues to be considered)	**Are there drug interactions with other drugs likely to be used for mania, i.e. buproprion and lithium?**	
Other comments or information not included above		
Primary reviewer Signature and Date		**July 22, 2002**
Secondary reviewer Signature and Date		**July 22, 2002**

CC: NDA 20-241 S-017 NDA 20-764 S-011HFD-850(P. Lee), HFD-860 (KavanaghR, BawejaR, MehtaM, MarroumP), HFD-120 (Ware), CDR (Barbara Murphy)

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/s/

Ron Kavanagh
7/22/02 02:15:34 PM
BIOPHARMACEUTICS

Raman Baweja
7/22/02 06:09:43 PM
BIOPHARMACEUTICS
Filing form

in healthy subjects. The study did not evaluate the effect of lithium on lamotrigine pharmacokinetics.

Recommendations: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 20-241 S-017 and NDA 20-764 S-011 to fulfill section 320 and 201.5 of 21 CFR, the information on the drug interactions between lamotrigine and lithium and bupropion are acceptable.

Labeling Recommendations: The following proposals by the sponsor are acceptable and recommended to be included in the drug interaction section of the Lamictal label

1) **Bupropion Added to Lamictal:** The pharmacokinetics of a 100-mg single dose of lamotrigine in 12 healthy volunteers were not changed by co-administration of bupropion at 300 mg/day starting 11 days before the lamotrigine dose

2) **Lamictal Added to Lithium:** The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by co-administration of 100 mg/day lamotrigine for 6-days

Kofi A. Kumi, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

CC: NDA 20-241(S017), NDA 20-764 (S011), HFD-120, HFD-860 (Kumi, Baweja, Sahajwalla, Mehta), Central Documents Room (Biopharm – CDR)

Table of Contents

What are the general attributes of lamotrigine?

Lamictal (lamotrigine), is an antiepileptic drug (AED) of the phenyltriazine class.
The chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine and the molecular weight is 256.09. It has a pKa of 5.7. Lamotrigine is slightly soluble in water (0.17 mg/mL at 25° C). The absolute bioavailability after oral administration is reported to be 98%. Lamotrigine is reported to be approximately 55% bound to plasma proteins at lamotrigine plasma concentrations from 1 to 10 µg/mL. Lamotrigine is metabolized predominantly by glucuronic acid conjugation with its major metabolite being an inactive 2-N-glucuronide, which is predominantly excreted via the urine. A small fraction (about 10% of an administered dose) is excreted in urine as unchanged lamotrigine. The apparent plasma clearance and plasma half-life in healthy volunteers is reported to be 0.44 mL/min/kg and 32.8 hours, respectively, after a single oral dose. Following multiple doses (150 mg bid), lamotrigine induced its own metabolism resulting in a 25% decrease in t ½ and a 37% increase in steady state apparent oral clearance. Dose linear increases in systemic lamotrigine exposure have been reported between a dose range of 50 – 400 mg. Lamictal tablets are approved and commercially available as 25 mg, 100 mg, 150 mg and 200 mg tablets. Lamictal chewable dispersible tablets are also approved and available commercially as 2 mg, 5 mg or 25 mg strengths.

Is there a clinically relevant pharmacokinetic interaction between lamotrigine and lithium?

Daily doses of 100mg of lamotrigine did not cause statistically significant change in the renal clearance of lithium. The 90% confidence intervals for the least squares mean ratios of CLr, Cmax, AUC and Ae between the two treatments were between 0.80 and 1.25. Clinically relevant effects on the pharmacokinetics of lithium by co–administration of lamotrigine are not expected. Dosage adjustments for lithium when co-administered with lamotrigine are not recommended. The effect of lithium on lamotrigine pharmacokinetics was not evaluated.

The submission contained a study that investigated whether multiple oral doses of lamotrigine affect the pharmacokinetics of multiple oral doses of lithium in healthy volunteers.
The study was a single center, open, balanced, 2-period, crossover design in 20 healthy volunteers. Treatment 1 consisted of 2g anhydrous lithium gluconate twice a day (12 hours apart) for 5 days with a single 2g anhydrous lithium gluconate dose on day 6. Treatment 2 consisted of 2g anhydrous lithium gluconate twice a day (12 hours apart) for 5 days with a single 2g anhydrous lithium gluconate dose on day 6. 100mg lamotrigine was administered once a day (morning) for 6 days. The volunteers received treatments in random order and the periods were separated by 2-week washout. The dosing regimen was expected to give mean day 5/6 trough lithium concentrations of 0.4 ± 0.10 mM and a day 6 peak concentration of 0.72 ± 0.12 mM. During the first five days, on lithium alone occasions, blood sample was obtained to determine serum lithium concentrations before each morning dose. On the combination treatment, blood samples were obtained to determine serum lithium concentrations before each dose (morning and evening) and a blood sample were taken before the lamotrigine dose to determine the trough plasma concentration of lamotrigine.

Median serum concentrations of lithium were slightly lower during the combination treatment than during lithium alone treatment as shown in figure 1. Mean Cmax and AUC of lithium on day 6 appeared to be slightly (7%) lower during the combination treatment than during the monotherapy. Mean CLr appeared to be comparable between the two treatments. The following

tables (Tables 1 and 2) contain a summary of lithium pharmacokinetic parameters computed after both treatments and the summary of the results of the statistical analysis of drug interaction

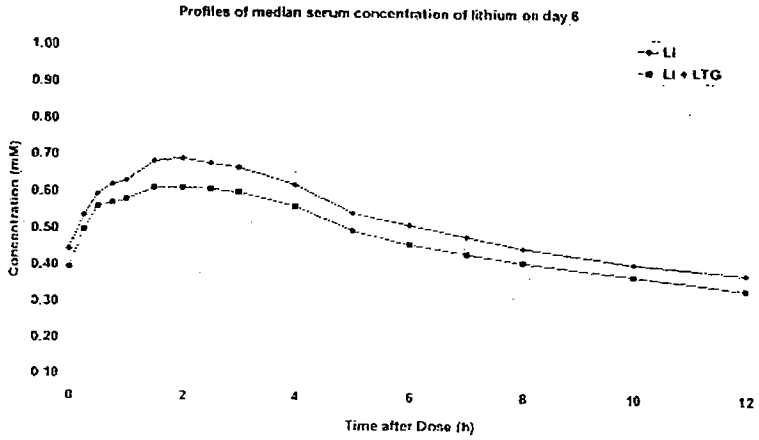

Figure 1

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Table 1: Summary of Lithium Pharmacokinetic Parameters

Parameter	Lithium	Lithium + Lamotrigine
	Mean ± SD (n=20)	
AUC(0-12) (mmol/h)	6.2 ± 0.776	5.75 ± 0.729
Cmax (mmol)	0.71 ± 0.080	0.65 ± 0.074
Tmax (h)	1.75 ± 0.791	1.69 ± 0.973
CLr (L/h)	1.83 ± 0.369	1.70 ± 0.302
Ae (0-12) (mmol)	11.21 ± 1.597	9.58 ± 1.343 (n=19)

Table 2: Summary of Results of Statistical Analysis

Parameter	Comparison of Test vs. Reference	Estimate of Group comparison (1)	90% Confidence Interval
Cmax (mM)	(Li+Ltg)/Li	0.92	(0.89, 0.96)
AUC (mM*h)	(Li + Ltg)/Li	0.92	(0.90, 0.94)
CLr (L/h)	(Li + Ltg)/Li	0.93	0.86, 1.00)
Ae (mmol)	(Li + Ltg)/Li	0.86	(0.80, 0.92)
Tmax (h)	(Li + Ltg) – Li	0.00	(-0.50, 0.75)

(1) The estimate is a ratio for all parameters except Tmax where the estimate is the median differences.

The potential effects of lamotrigine on the pharmacokinetics of lithium were evaluated. The sponsor used renal clearance of lithium as the primary endpoint for the analysis because lithium is removed from the systemic circulation almost completely by renal elimination. The 90% confidence intervals for the least squares mean ratios of CLr, Cmax, AUC and Ae between the two treatments were between 0.80 and 1.25. The study did not evaluate the effect of lithium on lamotrigine pharmacokinetics. The sponsor reported that both treatments were well tolerated and that there was no drug–related adverse events.

Is there a relevant pharmacokinetic interaction between lamotrigine and Bupropion?

The administration of bupropion hydrochloride (BUP, Wellbutrin SR) with Lamotrigine (LTG, Lamictal) resulted in no significant changes in AUC∞ , Cmax , t ½ , CL/F or tmax for LTG. Additionally, Cmax , t ½ , CLf , CLr and tmax for the inactive metabolite, LTG–gluconate, remained unaffected by BUP administration. The AUC∞ for LTG–gluc showed a small increase when LTG was administered with BUP. However, the small increase for the inactive metabolite is unlikely to have clinical significance. The effect of LTG on BUP pharmacokinetics at steady state was not evaluated.

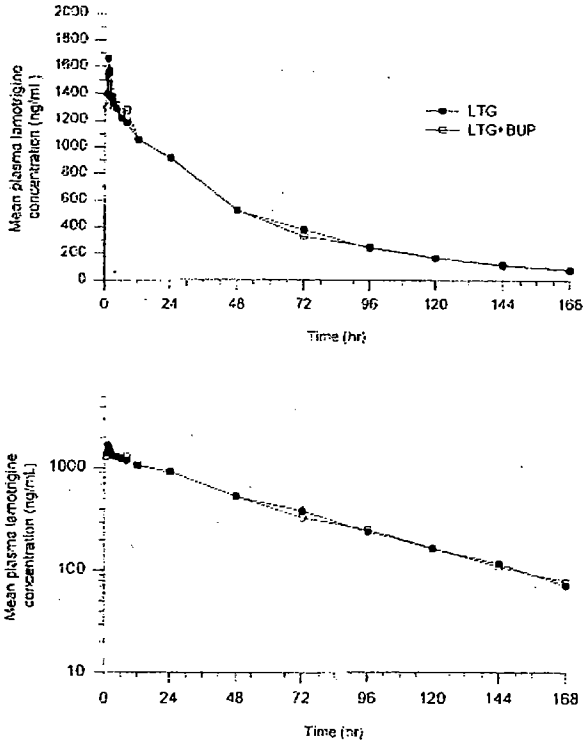
The submission contained a study that determined the effect of multiple doses of bupropion (BUP) on the pharmacokinetics of lamotrigine (LTG) and its major metabolite lamotrigine N 2 – glucuronide (LTG–gluc) following a single oral dose of LTG.

The study was a single center, open–label, randomized, two–way crossover in 12 volunteers. Volunteers were assigned to one of two treatments according to a randomization code. The treatments were separated by a 3-week washout period. Treatment A (LTG + BUP) was Bupropion lead-in phase days 1 – 14 (Wellbutrin SR 150 mg once daily days 1-3, followed by Wellbutrin SR 150 mg twice daily thereafter) with a single oral 100 mg dose of LTG on day 15. Bupropion dosing continued through day 21. Total treatment length of 3 weeks. Treatment B (LTG alone) was a single oral 100 mg dose of LTG. Total treatment length of 1 week

Mean LTG and LTG–gluc plasma concentration–time profiles (linear and semi–log) are displayed graphically in figures 2 and 3, respectively.

Figure 2

Plot of mean plasma lamotrigine concentration versus time



The mean plasma concentration-time profile for LTG-glucuronide is provided in figure 3

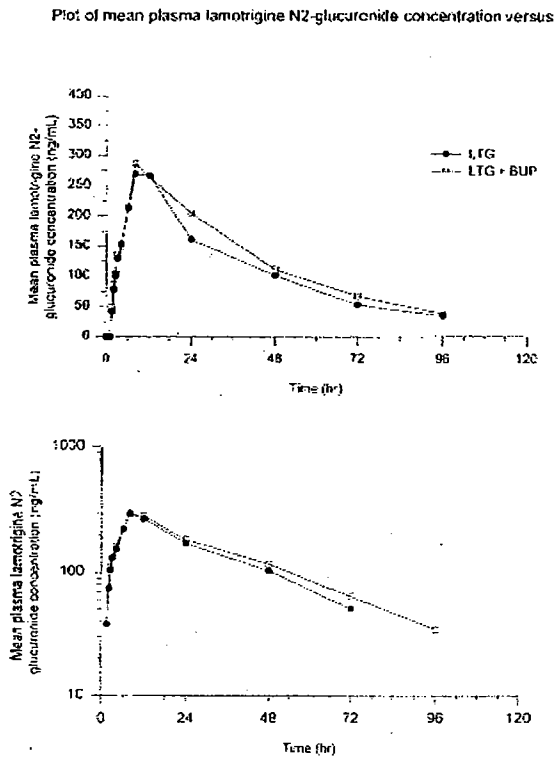


Figure 3

The geometric LS mean ratios (and 90% CI) used to compare the treatment groups are summarized in the following table. Lamotrigine pharmacokinetic parameters showed no statistical difference between treatment groups for any parameter.

Table 3: Treatment Comparison Results for LTG

Parameter	Treatment Comparison[a]	90% CI
AUClast (ng*hr/mL)	0.98	(0.92, 1.05)
AUC∞ (ng*hr/mL)	0.99	(0.93, 1.06)
Cmax (ng/mL)	0.95	(0.87, 1.04)
Cl/F (mL/min)	1.01	(0.94, 1.08)
T ½ (hr)	1.08	(0.99, 1.18)
Tmax (hr)	0.00	(-0.25, 0.50)

[a]the comparison is the geometric LS mean ratio between (LTG + BUP):LTG treatments for all parameters except tmax, where the comparison is the estimate of the median difference between the 2 treatments.

Table 4: Treatment Comparison Results for LTG-glucuronide

Parameter	Treatment Comparison[a]	90% CI
AUClast (ng*hr/mL)	1.11	(0.98, 1.26)
AUC∞ (ng*hr/mL)	1.15	(1.02, 1.31)
Cmax (ng/mL)	0.96	(0.87, 1.07)
Cl/F (mL/min)	1.05	(0.89, 1.25)
CLr (mL/min)	0.91	(0.79, 1.04)
T ½ (hr)	1.06	(0.84, 1.34)
Tmax (hr)	-0.03	(-2.00, 1.97)

[a]the comparison is the geometric LS mean ratio between (LTG + BUP):LTG treatments for all parameters except tmax, where the comparison is the estimate of the median difference between the 2 treatments.

Comparisons between the treatment groups revealed no statistically significant changes in any parameter, with the exception of LTG–gluc AUC∞. However, this change was very small and unlikely to have clinical significance.

Is there a dose/concentration response established for patients with bipolar disorder?

Concentration/dose response relationship was not established in bipolar patients in this efficacy supplement. The dose range recommended for the bipolar disorder is similar to that approved for epilepsy. However, the dosing regimen is different for both indications.

Appendix

Individual Study Reports

Study Title (Protocol SCAA1001, RM 1998/00281/00): A Randomized, Crossover Study to Evaluate the Pharmacokinetic Effect of Multiple Doses of Bupropion Hydrochloride (WELLBUTRIN SR) on a Single Oral Dose of Lamotrigine (LAMICTAL)

Background: Bipolar disorder is an illness characterized by recurrent episodes of mania and depression. Pharmacotherapy is the cornerstone of treatment and has dual objectives: to treat acute episodes and to decrease the incidence of their recurrence. Presently, lithium is the most widely recommended medication for acute and prophylactic treatment of bipolar disorder. Despite its widespread use, at least 30% of patients with a manic phase fail to respond to lithium or show severe side effects.

Lamotrigine (LTG) is an antiepileptic medication that works by blocking voltage sensitive sodium channels and inhibiting the release of excitatory neurotransmitters such as glutamate. Its efficacy as a [redacted] is currently being evaluated. LTG exhibits first order linear kinetics with the majority of the dose being recovered in the urine, predominantly as glucuronide conjugates. The bioavailability is 98%, plasma protein binding is 56% and the apparent volume of distribution is 1.2 ± 0.12 L/kg. The elimination half–life in healthy volunteers ranges from 25–35 hours.

Bupropion hydrochloride (BUP) is an antidepressant of the aminoketone class, unrelated to other known antidepressant agents. It is extensively metabolized by the cytochrome P450 enzyme system, with only 0.5% of the dose excreted unchanged. Bupropion plasma protein binding is approximately 80% and the mean elimination half life (± SD) is 21 (± 9) hours.

Metabolism of LTG occurs mainly via direct conjugation with glucuronic acid. Bupropion metabolism produces several phase I metabolites, a portion of which undergo further conjugation with glucuronic acid. Since both compounds share the common pathway of glucuronidation, co–administration may theoretically result in competition for enzyme availability, ultimately leading to altered metabolism and pharmacokinetics.

Study Objectives: 1) Determine the effect of multiple doses of bupropion (BUP) on the pharmacokinetics of lamotrigine (LTG) and its major metabolite lamotrigine N 2 – glucuronide (LTG–gluc) following a single oral dose of LTG. 2) Assess the safety and tolerability of this medication

Study Design: This was a single center, open–label, randomized, two–way crossover study in 12 healthy males and non–pregnant, non–lactating females. Six healthy male and six healthy female subjects aged 22–47 years and weighing 58.0–93.2 kg (BMI 22.8–28.7 kg/m ^{2}) were enrolled in the study. Of the six female subjects, two were of child bearing potential and using an acceptable method of contraception as outlined in the protocol. The remaining four female subjects were not of child bearing potential. Volunteers were assigned to one of two

treatments according to a randomization code. The treatments were separated by a 3 week washout period.

Treatment A (LTG + BUP): Bupropion lead-in phase days 1 – 14 (Wellbutrin SR 150 mg once daily days 1-3, followed by Wellbutrin SR 150 mg twice daily thereafter) with a single oral 100 mg dose of LTG on day 15. Bupropion dosing continued through day 21. Total treatment length of 3 weeks

Treatment B (LTG alone): Single oral 100 mg dose of LTG. Total treatment length of 1 week

Bupropion dosing was initiated with 150mg daily on days 1–3, and increased to 150mg twice daily for the remainder of the treatment period. There was an interval of at least eight hours between successive doses. On days 12–14, subjects reported to the research unit prior to the morning BUP dose for blood sampling of plasma BUP and metabolite concentrations. Subjects were admitted to the research unit on the evening of day 14 (one day prior to LTG dosing) and did not receive anything to eat after midnight. Lamotrigine and the morning dose of BUP were administered the following morning and food was allowed two hours after dosing. Blood samples (6mL) were collected into EDTA vacutainer tubes on each dosing occasion at the following times relative to LTG dosing: pre–dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours post–dose. Total urine was collected over the 24 hours following dosing. Subjects were discharged 24 hours following the LTG dose with the remaining six days supply of BUP and instructions for the collection of total urine produced over the next 24 hours. During the LTG alone treatment period, subjects were admitted to the research unit the evening prior to the LTG dose and did not receive anything to eat after midnight. Lamotrigine was administered the following morning and food was allowed two hours after dosing. Blood samples were collected over the next 24 hours and total urine was collected over 24 hours following dosing. Subjects were discharged 24 hours following the LTG dose with instructions for the collection of total urine produced over the next 24 hours. Subjects returned to the unit daily for collection of the remaining blood samples (48, 72, 96, 120, 144 and 168 hours).

During the LTG + BUP treatment period, blood samples were obtained to assess compliance with BUP therapy and ensure adequate exposure to BUP prior to LTG dosing. On days 12–14 of the LTG + BUP treatment period, subjects reported to the research unit prior to taking the morning dose of BUP. Blood samples (6 mL) were collected by venipuncture into vacutainer tubes containing heparin. On day 15 (when the subjects were in the research unit) the sample was drawn prior to the morning BUP dose and administration of LTG.

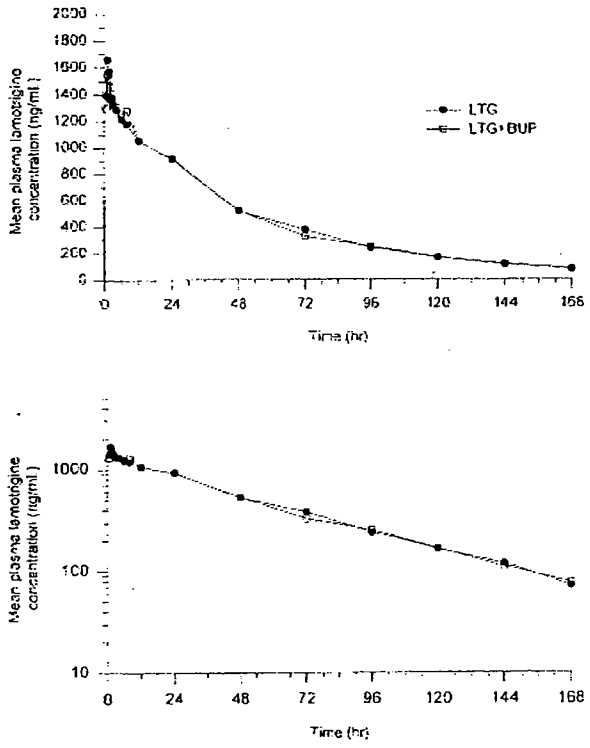
The study drugs used in the study were Lamotrigine (Lamictal 100 mg) chewable/dispersable tablets, batch no. 3568 and Bupropion (Wellbutrin SR 150 mg), batch no. 7F2359.

Analytical Method:

Data Analysis: Median and mean plasma LTG and LTG–gluc concentrations at each nominal time point were calculated as follows for each treatment group: All concentrations reported as BQL (below quantitation limit) were set to zero prior to summarization. Individual concentrations, if deemed to be clear outliers, were excluded from median and mean calculations. Pharmacokinetic parameters for LTG and LTG–gluc were estimated using model–independent analysis methods.

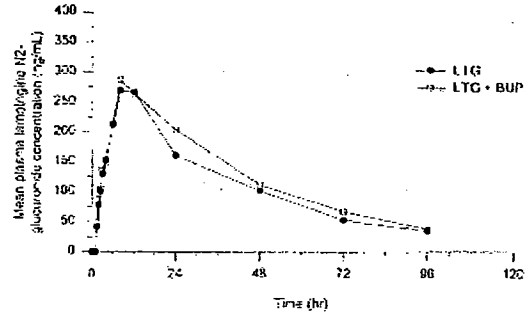
Results: Mean LTG and LTG–gluc plasma concentration–time profiles (linear and semi–log) are displayed graphically in the following figures.

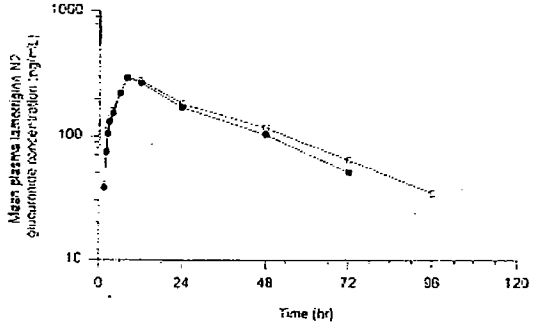
Plot of mean plasma lamotrigine concentration versus time



The mean plasma concentration-time profile for LTG-glucuronide is provided in the following figure

Plot of mean plasma lamotrigine N2-glucuronide concentration versus time





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Summary statistics for LTG pharmacokinetic parameters are shown in following table. The geometric mean (and 95% CI) for each parameter are Presented in the following table

Summary of LTG Pharmacokinetic Parameters

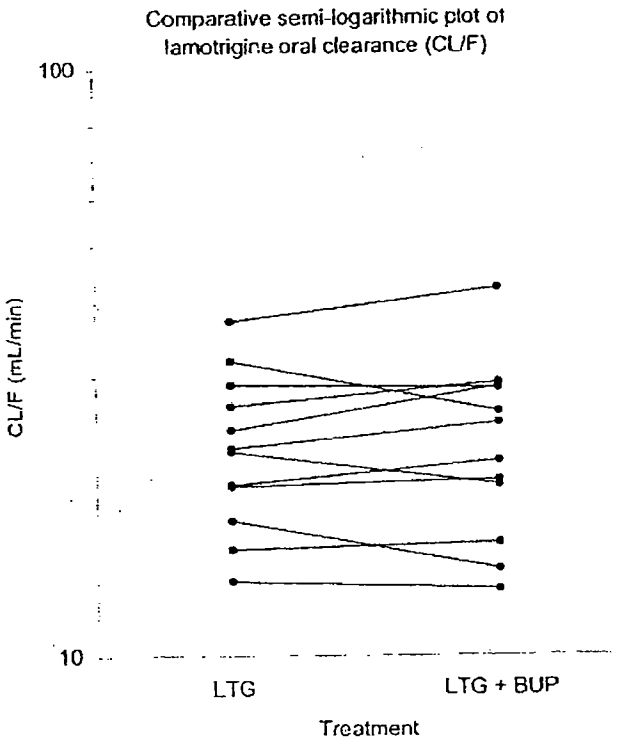
Parameter	Treatment	
	LTG (n=12)	LTG + BUP (n=12)
AUC_{last} (ng*hr/mL)		
Geometric mean	69372.6	68127.5
95% CI	(58419.9, 82377.3)	(55517.4, 83601.7)
AUC (ng*hr/mL)		
Geometric mean	74465.8	74032.8
95% CI	(61515.5, 89997.1)	(58940.9, 92988.9)
C_{max} (ng/mL)		
Geometric mean	1724.6	1635.2
95% CI	(1443.4, 2060.6)	(1425.7, 1875.6)
CL/F (mL/min)		
Geometric mean	22.40	22.51
95% CI	(18.52, 27.09)	(17.92, 26.28)
$t_{½}$ (hr)		
Geometric mean	39.68	42.97
95% CI	(33.82, 46.56)	(36.01, 51.28)
t_{max} (hr)		
Median	1.00	1.00
Range	(0.5, 6.0)	(0.5, 24)

Summary statistics for LTG-glucuronide pharmacokinetic parameters are shown in the following table.

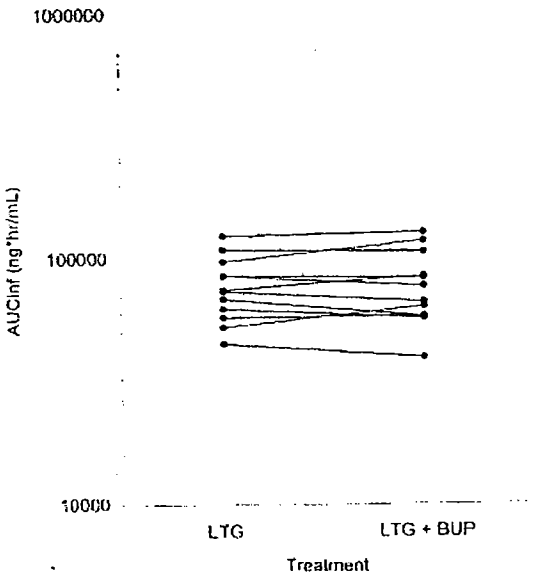
Parameter	Treatment	
	LTG (n=12)	LTG + BUP (n=12)
AUC_{last} (ng*hr/mL)		
Geometric mean	9881.8	10968.2
95% CI	(6960.5, 14029.3)	(7470.1, 16103.3)
AUC_{∞} (ng*hr/mL)		
Geometric mean	12130.4	13999.3
95% CI	(9302.9, 15817.2)	(11256.3, 17410.7)
C_{max} (ng/mL)		
Geometric mean	277.4	266.8
95% CI	(197.2, 390.0)	(183.6, 387.8)
CL_f (mL/min)		
Geometric mean	18.39	19.40
95% CI	(13.04, 25.95)	(14.53, 25.91)
CL_r (mL/min)		
Geometric mean	112.8	102.6
95% CI	(89.4, 142.4)	(79.9, 131.8)
$t_{½}$ (hr)		
Geometric mean	33.10	35.04
95% CI	(26.45, 41.43)	(26.68, 46.03)
t_{max} (hr)		
Median	8.00	8.00
Range	(8.0, 12.0)	(6.0, 12.0)

There does not appear to be significant difference in the geometric mean values for the pharmacokinetic parameters. There is large variability in the pharmacokinetic parameters, especially for AUC and Cmax, as indicated by the 95% confidence interval values.

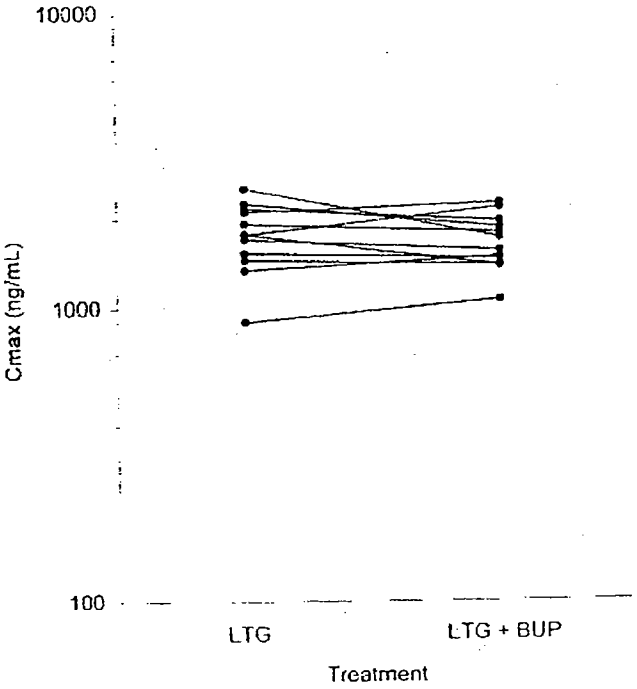
Comparative semi–log plots depicting the effect of different treatments on individual AUC∞ , Cmax , and CL/F for LTG are shown in following figures



Comparative semi-logarithmic plot of lamotrigine AUC_{inf}



Comparative semi-logarithmic plot of lamotrigine C_{max}



The geometric LS mean ratios (and 90% CI) used to compare the treatment groups are summarized in the following table. LS means (or medians in the case of tmax) for LTG pharmacokinetic parameters showed no statistical difference between treatment groups for any parameter.

Treatment Comparison Results for LTG

Parameter	Treatment Comparison[a]	90% CI
AUC_{last} (ng*hr/mL)	0.98	(0.92, 1.05)
AUC_{∞} (ng*hr/mL)	0.99	(0.93, 1.06)
C_{max} (ng/mL)	0.95	(0.87, 1.04)
CL/F (mL/min)	1.01	(0.94, 1.08)
$t_{½}$ (hr)	1.08	(0.99, 1.18)
t_{max} (hr)	0.00	(–0.25, 0.50)

[a] the comparison is the geometric LS mean ratio between (LTG + BUP):LTG treatments for all parameters except t_{max}, where the comparison is the Hodges–Lehmann estimate of the median difference between the 2 treatments.

Results from the treatment comparison analysis on log transformed parameters for LTG–gluc is provided in the following table. The geometric LS mean ratios (and 90% CI) used to compare the treatment groups are contained in the following table.

Treatment Comparison Results for LTG-glucuronide

Parameter	Treatment Comparison[a]	90% CI
AUC_{last} (ng*hr/mL)	1.11	(0.98, 1.26)
AUC_{∞} (ng*hr/mL)	1.15	(1.02, 1.31)
C_{max} (ng/mL)	0.96	(0.87, 1.07)
CL_f (mL/min)	1.05	(0.89, 1.25)
CL_r (mL/min)	0.91	(0.79, 1.04)
$t_{½}$ (hr)	1.06	(0.84, 1.34)
t_{max} (hr)	–0.03	(–2.00, 1.97)

[a] the comparison is the geometric LS mean ratio between (LTG + BUP):LTG treatments for all parameters except t_{max}, where the comparison is the Hodges–Lehmann estimate of the median difference between the 2 treatments.

Comparison of the geometric LS means (or medians in the case of Tmax) for LTG–gluc pharmacokinetic parameters showed no statistical difference between treatment groups for AUClast , Cmax , CLf , CLr , t ½, or tmax . However, the 90% CI for the geometric LS mean ratio between treatment groups for LTG–gluc AUClast and AUC∞ were slightly above the 90% confidence limits of 80 to 125. The sponsor reported that the treatment difference observed for this inactive metabolite is unlikely to have clinical significance.

Pharmacokinetic conclusions: Pharmacokinetic parameters for LTG and LTG–gluc were determined following a single, oral 100mg dose of LTG with and without concurrent BUP administration. The sponsor reported that comparisons between the treatment groups revealed no statistically significant changes in any parameter, with the exception of LTG–gluc AUC∞. However, this change was very small and unlikely to have clinical significance.

One subject had a much larger tmax for LTG during both treatment periods compared to other subjects (24 hours versus the mean value of 2.8 hours in the LTG treatment; and 6 hours versus the mean value of 1.5 hrs in the LTG + BUP treatment). The sponsor reported that the delayed absorption in this subject contributed to the large ranges observed for LTG tmax (0.5 to 24 hours for the LTG treatment, and 0.5 to 6 hours for the LTG + BUP treatment). The increased tmax value in the same subject, regardless of treatment, suggests that the delayed LTG absorption was subject–related, rather than treatment–related.

Safety conclusions: The most common AEs were headache, insomnia, nausea, fatigue and blurred vision. All AEs were mild in intensity and resolved prior to the end of the study. There was no SAE reported, and all AEs resolved prior to study completion. There was no clinically significant change in laboratory data or vital sign measurements from screening to follow–up, or during either treatment period. No subject was discontinued from the study because of an AE.

Summary: The primary objective of this study was to determine the effect of multiple doses of BUP on the pharmacokinetics of LTG and LTG–gluc following a single oral 100mg dose of LTG. The administration of BUP with LTG resulted in no significant changes in AUC∞ , Cmax , t ½ , CL/F or tmax for LTG. Additionally, Cmax , t ½ , CLf , CLr and tmax for LTG–gluc remained unaffected by BUP administration. The AUC∞ for LTG–gluc showed a small increase when LTG was administered with BUP. However, the small increase for this inactive metabolite is unlikely to have clinical significance.

Reviewer's comments: *Generally, the reviewer agrees with the sponsor's conclusions. Extent of exposure for LTG-gluc as measure by AUC were not equivalent as determined by the 90% CI for AUClast and AUC∞. However, since this is an inactive metabolite, the reviewer agrees with the sponsor's conclusion that this will not be of clinical significance. The study did not evaluate the effect of LTG on BUP pharmacokinetics at steady state.*

Study Title (Protocol SCAB1001; Report PM 1998/00008/00): Report for a study to investigate whether multiple oral doses of lamotrigine affect the pharmacokinetics of multiple oral doses of lithium in healthy volunteers.

Objective: To determine the influence of multiple doses of lamotrigine on the pharmacokinetics of multiple oral doses of lithium

Study Design: This was a single center, open, balanced, 2-period, cross-over design in which 20 healthy volunteers, ages 18 to 45 years, received treatments in random order separated by 2 week wash-out period. The study was conducted in France

Treatment 1: 2g anhydrous lithium gluconate twice a day (12 hours apart) for 5 days with a single 2g anhydrous lithium gluconate dose on day 6.

Treatment 2: 2g anhydrous lithium gluconate twice a day (12 hours apart) for 5 days with a single 2g anhydrous lithium gluconate dose on day 6. 100mg lamotrigine once a day (morning) for 6 days.

The dosing regimen was expected to give mean day 5/6 trough lithium concentrations of 0.4 ± 0.10 mM and a day 6 peak concentration of 0.72 ± 0.12 mM. Each dose of lithium was administered only when the concentration from the previous dose was known.

The volunteers had a creatinine clearance ≥ 80 mL/min (Cockroft and Gault formula). 100mg lamotrigine (one 100 mg lamotrigine dispersible tablet once a day) and 2g anhydrous lithium gluconate (one 10 mL ampoule of Neurolithium twice a day) were administered with 200 mL water during a standard meal (breakfast or dinner).

During the first five days: On the lithium alone occasion, blood sample (5 mL) was obtained to determine serum lithium concentrations before each morning dose. On the combination treatment, blood samples (5mL) were obtained to determine serum lithium concentrations before each dose (morning and evening) and a blood sample (10mL) were taken before the lamotrigine dose to determine the trough plasma concentration of lamotrigine.

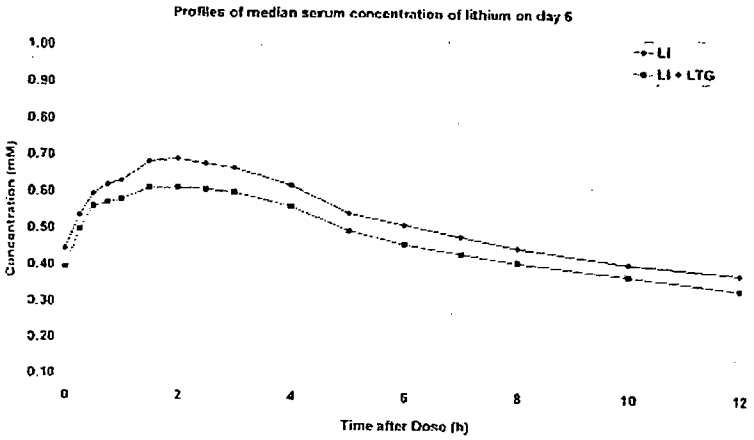
On day 6: Blood samples (5 mL) were taken for lithium assay pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hours after dosing. A blood sample (10 mL) was taken before the lamotrigine dose to determine the trough plasma concentration of lamotrigine. All urine was collected for lithium assay for 12 hours after dosing. There was a wash-out period of two weeks between the 2 treatments.

Analytical Method:

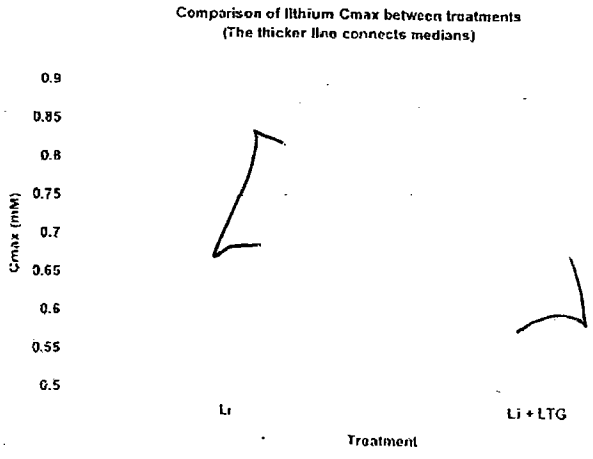
Data Analysis: Pharmacokinetic parameters of lithium were calculated using non–compartmental methods following lithium administration on day 6 of both treatments. The maximum plasma concentration and the time of maximum concentration were read directly from the plasma concentration–time profile. The area under the plasma concentration time curve for 12 hours after dosing were obtained by linear trapezoidal summation. Renal

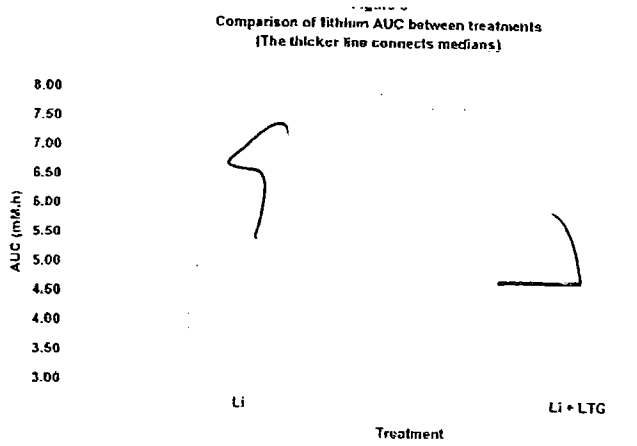
clearance was calculated as the ratio Ae(0–12) /AUC(0–12) , where Ae is amount excreted unchanged.

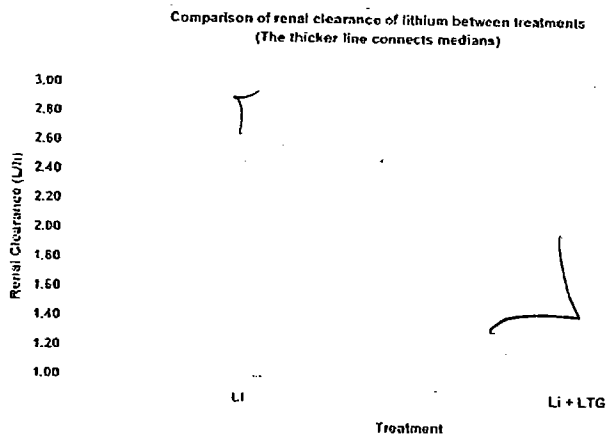
Pharmacokinetic Results: Median trough plasma concentrations of lamotrigine and the concentrations in the majority of subjects appeared to have reached steady–state by the 6th day of the combination treatment. The median trough serum concentrations of lithium and the concentrations in the majority of subjects appeared to have reached the steady–state by day 6 of the lithium alone treatment and after day 6 in the lithium plus lamotrigine treatment. Median serum concentrations of lithium were slightly lower during the combination treatment than during lithium alone treatment as shown in the following figure.



Comparison of Cmax, AUC and CLr in individual subjects are provided in the following figures







Median Cmax and AUC of lithium on day 6 appeared to be slightly lower during the combination treatment than during the monotherapy. Median CLr appeared to be comparable between the two treatments. The following tables contain a summary of lithium pharmacokinetic parameters computed after both treatments and the summary of the results of the statistical analysis of drug interaction

Summary of Lithium Pharmacokinetic Parameters

Parameter	Lithium	Lithium + Lamotrigine
	Mean ± SD (n=20)	
AUC(0-12) (mmol/h)	6.2 ± 0.776	5.75 ± 0.729
Cmax (mmol)	0.71 ± 0.080	0.65 ± 0.074
Tmax (h)	1.75 ± 0.791	1.69 ± 0.973
CLr (L/h)	1.83 ± 0.369	1.70 ± 0.302
Ae (0-12) (mmol)	11.21 ± 1.597	9.58 ± 1.343 (n=19)

Summary of Results of Statistical Analysis

Parameter	Comparison of Test vs. Reference	Estimate of Group comparison (1)	90% Confidence Interval
Cmax (mM)	(Li+Ltg)/Li	0.92	(0.89, 0.96)
AUC (mM*h)	(Li + Ltg)/Li	0.92	(0.90, 0.94)
CLr (L/h)	(Li + Ltg)/Li	0.93	0.86, 1.00)
Ae (mmol)	(Li + Ltg)/Li	0.86	(0.80, 0.92)
Tmax (h)	(Li + Ltg) – Li	0.00	(-0.50, 0.75)

(1) The estimate is a ratio for all parameters except Tmax where the estimate is the median differences.

The 90% confidence intervals for the geometric least squares mean ratios of the pharmacokinetic parameters fall between 0.80 and 1.25, hence, there is no significant difference in these parameters between the treatments.

Safety conclusions: The sponsor reported that both treatments were well tolerated in healthy volunteers. The sponsor reported no drug–related adverse events. The sponsor reported only one adverse event of moderate intensity (pruritic skin rash) during the combination treatment with lamotrigine and lithium. This adverse event was considered as non drug–related by the investigator. The sponsor reported that there was no evidence of any clinically significant study drug effect on laboratory data, vital signs or ECG data.

Summary and conclusions: The study was undertaken to assess the potential effects of lamotrigine on the pharmacokinetics of lithium. The sponsor reported that since lithium is removed from the systemic circulation almost completely by renal elimination, renal clearance of lithium was used as the primary endpoint for the analysis. Daily doses of 100mg of lamotrigine did not cause a statistically significant change in the renal clearance of lithium. The 90% confidence intervals for the least squares mean ratios of CLr, Cmax, AUC and Ae between the two treatments were between 0.80 and 1.25. The sponsor reported a lack of clinically relevant effects on the pharmacokinetics of lithium by co–administration of lamotrigine in healthy subjects. According to the sponsor, this suggests that there is no need to alter lithium dosage when lamotrigine is added to lithium therapy.

Reviewer's comments: *The reviewer agrees with the sponsor's conclusion of no significant difference in lithium pharmacokinetics after co-administration with lamotrigine. However, the 90% confidence intervals did not include 1 except Clrenal, which suggests a trend towards lower exposures of lithium after co-administration of lithium and lamotrigine. The study did not evaluate the effect of lithium on lamotrigine pharmacokinetics.*

Figure 7
Comparison of renal clearance of lithium between treatments
(The thicker line connects medians)

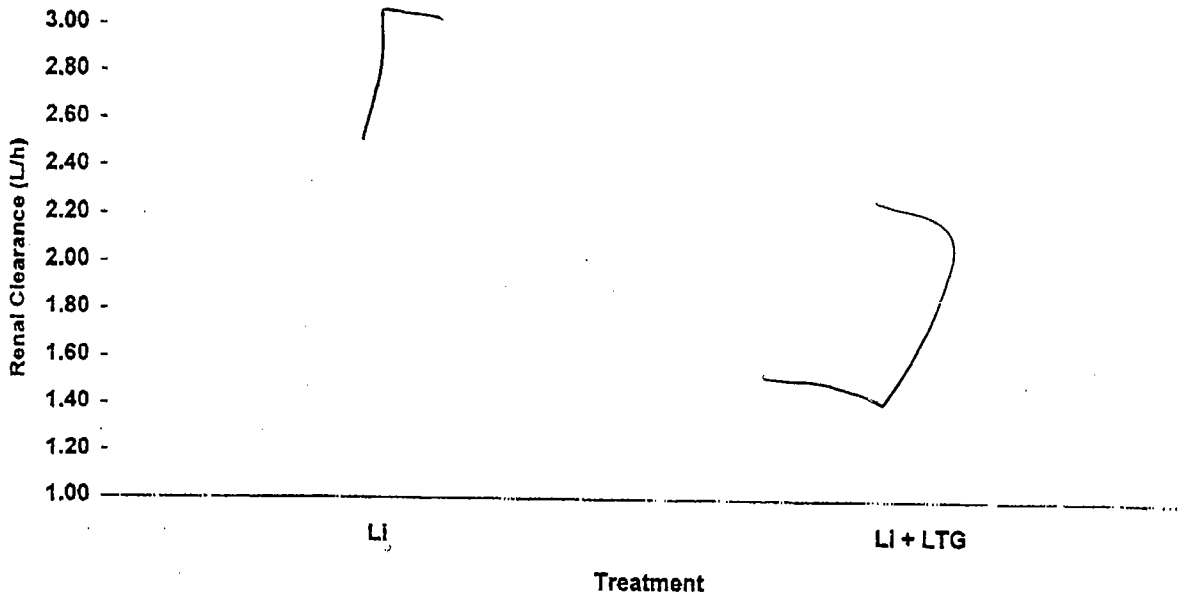


Figure 6
Comparison of lithium AUC between treatments
(The thicker line connects medians)

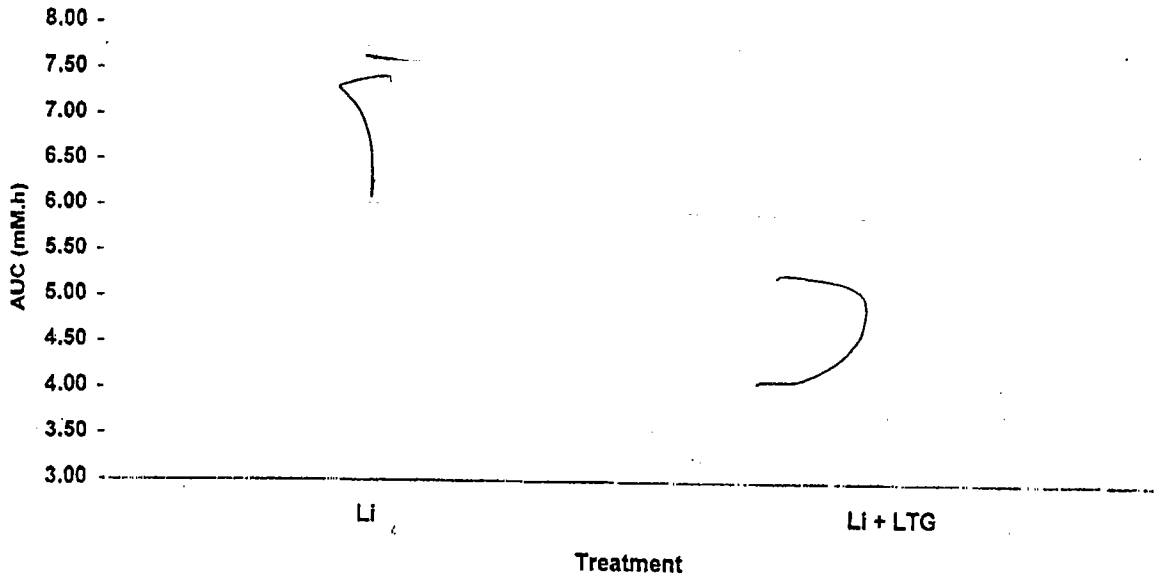


Figure 5
Comparison of lithium Cmax between treatments
(The thicker line connects medians)

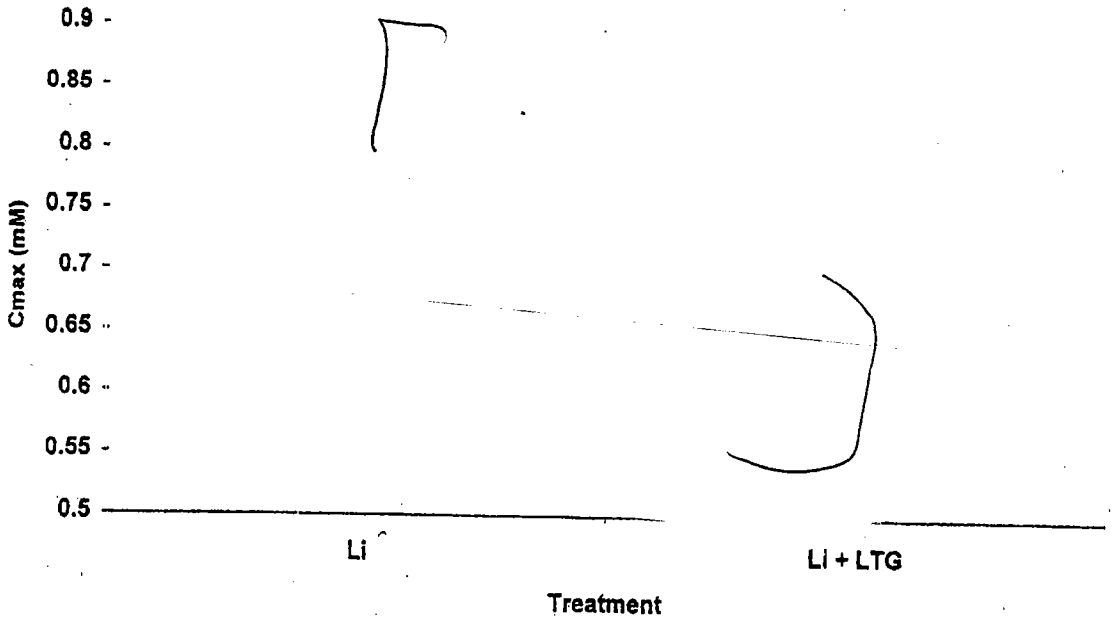
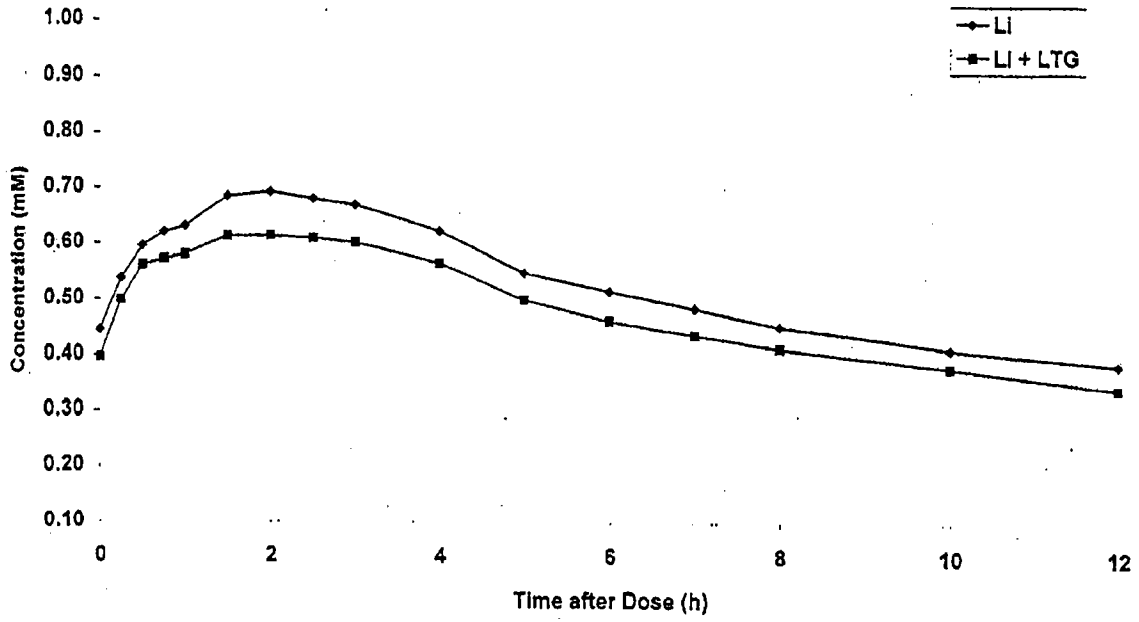


Figure 4
Profiles of median serum concentration of lithium on day 6



PROTOCOL: scab1001
POPULATION: All Subjects

Listing 11
Listing of Lithium Pharmacokinetic Parameter Values

Subject	Period	Treatment	AUC(0-12) (mmol/h)	Cmax (mmoL)	Tmax (h)	CLr (L/h)	Ae(0-12) (mmol)
5301	1	Li	4.87	0.55	2.50		
	2	Li+Ltg	4.79	0.55	1.00		
5302	1	Li+Ltg	3.99	0.52	2.50		
	2	Li	4.71	0.57	1.00		
5303	1	Li	5.56	0.63	2.00		
	2	Li+Ltg	5.29	0.60	3.00		
5304	1	Li+Ltg	7.16	0.78	0.75		
	2	Li	7.14	0.75	2.00		
5305	1	Li	6.69	0.73	1.50		
	2	Li+Ltg	6.03	0.70	0.50		
5306	1	Li+Ltg	5.51	0.61	0.50		
	2	Li	6.59	0.76	1.50		
5307	1	Li+Ltg	6.00	0.68	2.00		
	2	Li	6.60	0.74	2.50		
5308	1	Li	5.52	0.67	3.00		
	2	Li+Ltg	5.66	0.68	0.75		
5309	1	Li+Ltg	6.32	0.75	1.50		
	2	Li	6.92	0.80	2.00		
5310	1	Li	6.42	0.66	2.50		
	2	Li+Ltg	5.83	0.60	0.75		
5311	1	Li+Ltg	6.75	0.71	3.00		
	2	Li	6.98	0.78	2.50		
5312	1	Li	6.41	0.72	2.00		
	2	Li+Ltg	5.60	0.65	1.50		
5313	1	Li	6.40	0.71	2.00		
	2	Li+Ltg	5.84	0.64	3.00		
5314	1	Li	5.44	0.65	0.50		
	2	Li+Ltg	5.03	0.58	2.00		
5315	1	Li+Ltg	5.64	0.65	2.00		
	2	Li	5.96	0.72	2.00		
5316	1	Li+Ltg	6.76	0.73	2.50		
	2	Li	7.63	0.87	0.50		
5317	1	Li	6.86	0.78	0.75		

PROTOCOL: scabi001
POPULATION: All Subjects

Listing 11
Listing of Lithium Pharmacokinetic Parameter Values

Subject	Period	Treatment	AUC(0-12) (mmol/h)	Cmax (mmoL)	Tmax (h)	CLr (L/h)	Ae(0-12) (mmol)
5317	2	Li+Ltg	6.28	0.65	3.00		
5319	1	Li	6.02	0.72	1.50		
	2	Li+Ltg	5.11	0.56	0.50		
5320	1	Li+Ltg	5.52	0.77	0.50		
	2	Li	5.38	0.61	2.50		
5321	1	Li+Ltg	5.89	0.68	2.50		
	2	Li	6.48	0.77	0.25		

PROTOCOL: scab1001
POPULATION: All Subjects

Table 8
Summary of Lithium Pharmacokinetic Parameter Values

Statistic or Category	Treatment	
	Li	Li+Ltg
CLr (L/h)		
N	20	19
Mean	1.83	1.70
Std.Dev.	0.369	0.302
Median	1.71	1.74
Minimum	1.37	1.18
Maximum	3.00	2.23
Coef.Var.	20.20	17.77
Mean logs	0.5857	0.5142
SD logs	0.1795	0.1855
Geo.Mean	1.80	1.67
95% CI L	1.65	1.53
95% CI U	1.95	1.83
Tmax (h)		
N	20	20
Mean	1.75	1.69
Std.Dev.	0.791	0.973
Median	2.00	1.75
Minimum	0.25	0.50
Maximum	3.00	3.00
Coef.Var.	45.18	57.65

PROTOCOL: scabl1001
POPULATION: All Subjects

Table 8
Summary of Lithium Pharmacokinetic Parameter Values

	Statistic or Category	Treatment	
		Li	Li+Ltg
AUC(0-12) (mmol/h)			
	N	20	20
	Mean	6.23	5.75
	Std.Dev.	0.776	0.729
	Median	6.42	5.75
	Minimum	4.71	3.99
	Maximum	7.63	7.16
	Coef.Var.	12.46	12.68
	Mean logs	1.8215	1.7412
	SD logs	0.1291	0.1320
	Geo.Mean	6.18	5.70
	95% CI L	5.82	5.36
	95% CI U	6.57	6.07
Cmax (mmol)			
	N	20	20
	Mean	0.71	0.65
	Std.Dev.	0.080	0.074
	Median	0.72	0.65
	Minimum	0.55	0.52
	Maximum	0.87	0.78
	Coef.Var.	11.30	11.23
	Mean logs	-0.3495	-0.4300
	SD logs	0.1163	0.1136
	Geo.Mean	0.71	0.65
	95% CI L	0.67	0.62
	95% CI U	0.74	0.69
Ae(0-12) (mmol)			
	N	20	19
	Mean	11.21	9.58
	Std.Dev.	1.597	1.343
	Median	11.04	10.00
	Minimum	8.79	7.14
	Maximum	16.17	11.64
	Coef.Var.	14.25	14.01
	Mean logs	2.4078	2.2504
	SD logs	0.1346	0.1450
	Geo.Mean	11.11	9.49
	95% CI L	10.43	8.85
	95% CI U	11.83	10.18

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PROTOCOL: scab1001
POPULATION: All Subjects

Table 9
Summary of Results of Analysis of Drug Interaction

Parameter	Comparison of Test vs. Reference	Estimate of Test Group [1]	Estimate of Reference Group [1]	Estimate of Group Comparison [2]	90% Confidence Interval
AE (mmol)	(Li+Ltg)/Li	9.54	11.11	0.86	(0.80, 0.92)
AUC (mM.h)	(Li+Ltg)/Li	5.70	6.18	0.92	(0.90, 0.94)
CL/F (l/h)	(Li+Ltg)/Li	1.67	1.80	0.93	(0.86, 1.00)
Cmax (mM)	(Li+Ltg)/Li	0.65	0.71	0.92	(0.89, 0.96)
Tmax (h)	(Li+Ltg)-Li	1.75	2.00	0.00	(-0.50, 0.75)

[1] The estimate is the geometric least squares mean for all parameters except Tmax where the estimate is the median.
[2] The estimate is a ratio for all parameters except Tmax where the estimate is the Hodges-Lehman estimate of the median differences.
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Raman Baweja
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