CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

Memo for the File

NDA:	22-251	Submission Date:	November 28, 2007
Brand Name:	Lamictal®	Generic Name:	Lamotrigine
Dosage Form:	Orally Disintegrating Tablets	Indication:	Treatment of Seizure
Dosage	25, 50, 100, and 200 mg	Sponsor:	GlaxoSmithKline
NDA type:	505(b)(1)		
Reviewer:	Carol Noory	Team Leader:	Veneeta Tandon, Ph.D.
OCP Division:	DCP-1, HFD-860	OND Division:	Neurology HFD-120

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BACKGROUND

The current NDA seeks approval of Lamictal® 25 mg, 50 mg, 100 mg and 200 mg orally disintegrating tablets [ODT]. In support of the application, the Sponsor conducted a pivotal four-arm parallel-group bioequivalence study [LBI108617] in 216 healthy male and female volunteers (54 assigned to each treatment). This study was designed to demonstrate the bioequivalence of the ODT to the Lamictal® IR tablet and to determine the effect of food and water on the ODT. Analysis of the data submitted by the sponsor determined that the ODT was bioequivalent relative to the Lamictal IR Tablet pending the results of the DSI inspection (OCP review submitted to DFS 8/28/2008).

RESULTS OF DSI INSPECTION

On 9/8/08, DSI reported their finding to Division of Neurology. Following FDA's audit of the bioanalytical site (8/25-28/08) for this NDA, DSI issued a Form 483 to GlaxoSmithKline R&D, Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetic (GSK-DMPQ) located at Research

Triangle Park, North Carolina. DSI found that there were significant issues regarding the conduct of the bioanalysis of the data from the pivotal study. These issues are briefly summarized here:

1. Reconstruction of the study results was not possible because the firm did not retain the electronic data and audit trail generated by the chromatography acquisition and integration software (PDF copies of the chromatograms were retained)
2. Data from original runs that were rejected and reanalyzed were not retained. The reason for re-integration of some of the runs was not apparent because the electronic data was not preserved.
3. Some runs with questionable QC results were not rejected, they were modified or reintegrated. The firm did not document why the reintegration was necessary. The inspection found that integration parameter sets used in 25% of the runs were modified or changed during the run.

Based on the above findings, DSI concluded that the accuracy of 37 % of analytical runs could not be assured. Table 1 lists the analytical runs that involved different integration parameters compared to the first analytical run.

Analytical Run
LBI108617HUSE004
LBI108617HUSE005
LBI108617HUSE008
LBI108617HUSE014
LBI108617HUSE016
LBI108617HUSE018
LBI108617HUSE022
LBI108617HUSE023
LBI108617HUSE024
LBI108617HUSE026
LBI108617HUSE027
LBI108617HUSE035
LBI108617HUSE040
LBI108617HUSE041
LBI108617HUSE045
LBI108617HUSE046
LBI108617HUSE047
LBI108617HUSE048
LBI108617HUSE049
LBI108617HUSE050

RE-ANALYSIS OF DATA

Subsequent to the inspection, this reviewer re-analyzed the data eliminating the runs identified in the DSI report as having questionable results. The results of the original data and the data eliminating suspect runs are given below. The study treatments are identified as:

C: 200mg ODT disintegrated/fasted
D: 200 mg IR tablet fasted
E: ODT disintegrated/fed
F: ODT swallowed with water/fasted

Both the original and re-evaluated pharmacokinetic parameters are shown in the following table.

PK parameters (original and re-evaluated)								
	N	**Original**	**N**	**Re-evaluated**	**N**	**Original**	**N**	**Re-evaluated**
TRT		**AUC $_{(0\text{-}INF)}$ (µg•h/mL)**				**Cmax (µg/mL)**		
C	54	161 (43)	32	158 (50)	54	3.4 (20)	32	3.4 (22)
D	54	177 (37)	33	164 (39)	54	3.7 (22)	33	3.6 (23)
E	54	160 (45)	34	159 (60)	54	2.9 (19)	34	2.8 (20)
F	53	168 (38)	33	165 (37)	53	3.5 (23)	33	3.3 (20)

(%CV) is given in ()

The geometric mean ratio and 90% confidence intervals for the original and re-evaluated data are presented in the following table.

Original Results						
		AUC (0-inf)			**Cmax**	
		GM Ratio	90% CI		GM Ratio	90% CI
C/D		91.0	80.3, 103.1		94.1	88.1, 100.6
E/C		99.5	87.8, 112.8		84.3	78.9, 90.1
F/C		104.1	91.8, 118.1		100.5	94.0, 107.4
Re-evaluated Results						
		AUC (0-inf)			**Cmax**	
		Geometric Mean Ratio	90% Confidence Intervals		Geometric Mean Ratio	90% Confidence Intervals
C/D		96.2	81.9, 113.0		95.2	87.31, 103.97
E/C		100.4	85.6, 117.3		83.53	76.5, 93.9
F/C		104.34	88.9, 122.6		97.65	89.4, 106.5

POWER TO DETERMINE BIOEQUIVALENCE

In the original submission, the sponsor had stated that the number of subjected needed to determine bioequivalence based on the 90% confidence interval was determined using the between subject %CV of some previous studies. Based on the highest between-subject CV observed in other lamotrigine trials (32.7% and 20.4%) for AUC(0–∞) and Cmax, respectively, it was determined that a sample size of 50 evaluable subjects per arm would have a power of over 90% to demonstrate bioequivalence or lack of food and water effects for either primary pharmacokinetic parameter, if the true ratio of the geometric means of the test and reference treatments was equal to one."

The summary of the between-subject coefficient of variation for the primary PK parameters using all 54 subjects and the re-evaluated data using 32-34 subjects is shown in the following table.

Summary of Between-Subject Coefficient of Variation for Primary PK parameters				
Full study (54 subjects/regimen)				
Parameter	Regimen C	Regimen D	Regimen E	Regimen F
AUC (0-inf)	43.4	37.4	44.9	37.9
Cmax	20.0	22.0	19.3	22.9
Re-evaluated data (32, 33 or 34 subjects/regimen)				
Parameter	Regimen C	Regimen D	Regimen E	Regimen F
AUC (0-inf)	50.3	39.3	59.7	36.9
Cmax	22.2	23.4	20.0	20.3

Donald Schuirmann, a biomedical statistician with the Office of Translational Science, was asked to evaluate the ability of the reduced number of subjects to determine bioequivalence of the Lamictal ODT compared to the Lamictal IR Tablet. His evaluation is attached (Attachment 1).

CONCLUSION

Re-evaluating the data with the reduced number of subjects indicate that the Lamictal ODT is bioequivalent to the Lamictal IR tablet. Geometric mean ratios and 90% confidence intervals were

similar to the original analysis for all treatment regimens. However, the impact on the bioequivalence analysis of the study if the integration parameters were not changed in the bioanalysis of some subjects cannot be determined.

SIGNATURES

Reviewer: Carol Noory
Team Leader: Veneeta Tandon

cc list: DFS: NDA 22-251
HFD-860: *(NooryC, TandonV, UppoorR, MehtaM)*
HFD-120: *(KatzR, WareJ, SheridanP, HershkowitzN)*

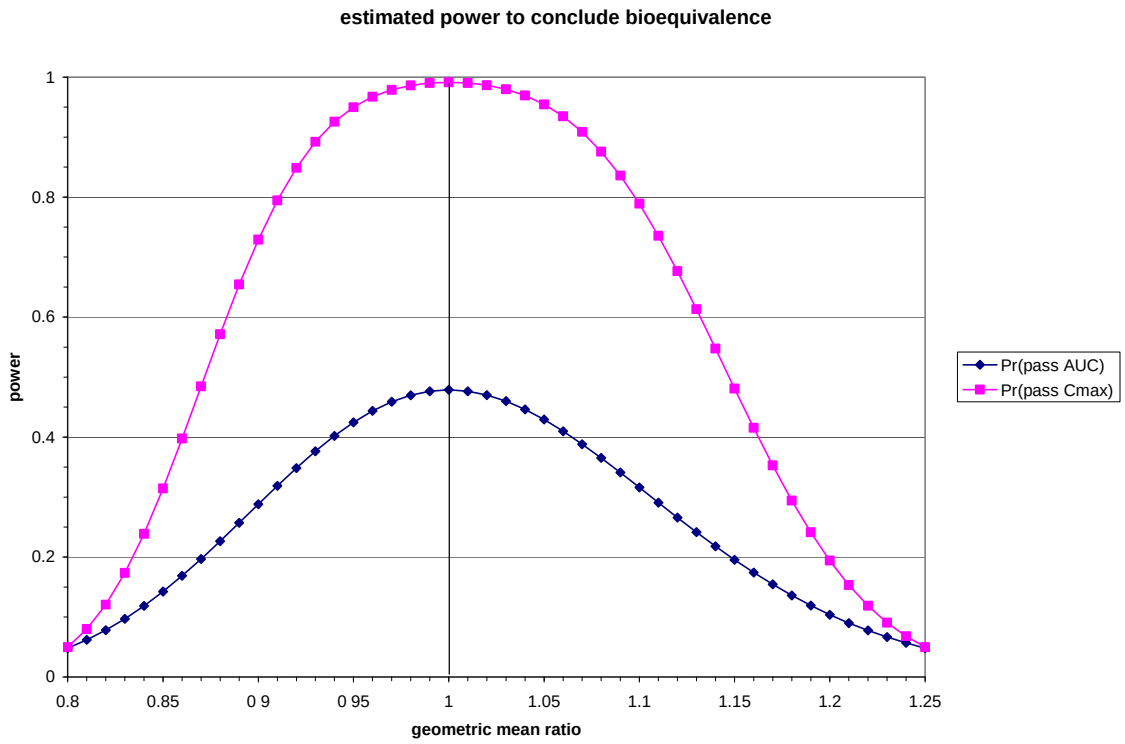
ATTACHMENT 1

E-mail Response from Donald Schuirmann to Veneeta Tandon dated September 24, 2008

The estimated coefficients of variation (CV's) for products C and D from the study (taken from **Original Data Table 1: Summary of Between-Subject Coefficient of Variation for Primary PK parameters** in the document you sent to me this morning) are

	product C	product D
AUC	43.44%	37.37%
Cmax	20.035%	21.991%

To my eye, 43.44% does not look substantially different from 37.37%, nor does 20.035% look substantially different from 21.991% (in both cases, the estimates are not statistically significantly different, testing at the two-sided 0.05 level of significance.) For that reason, I pooled the product C and product D estimates into a common estimate, and got 40.439% for the AUC CV and 21.049% for the Cmax CV. Given these variability estimates, I calculated the estimated power of the average bioequivalence test, which I present in this figure:



Some values from this graph are:

geometric mean ratio	prob. of passing for AUC	prob. of passing for Cmax
1.0	0.478660	0.991405
0.95 or 1.05263	0.424440	0.949942
0.9 or 1.11111	0.287994	0.729265
0.85 or 1.17647	0.142434	0.314235
0.8 or 1.25	0.048288	0.050000

Let us restrict our attention to AUC, since it is apparent that even with 32 subjects for product C and 33 subjects for product D the study had very good power for Cmax. As required, the probability of passing is no more than 0.05 if the geometric mean ratio is as low or lower than 0.8 or as high or higher than 1.25 (for AUC, it is actually a little less than 0.05, namely 0.048288.) So, under the reasoning of statistical hypothesis testing, the chance that a study will pass for a AUC, if in fact the products are not average bioequivalent for AUC, is "low" (with "low" defined as "no more than 0.05".) So if we see a study that passes the test for AUC, we seek a "more likely" explanation than "the products are not average bioequivalent, but an event with low probability occurred." This "more likely" explanation is "the products are average bioequivalent."

It is possible to have a situation where variability is so great and/or sample size is so low that the power curve is essentially flat, and passing the test when the geometric mean ratio is 1.0 is not substantially more likely than passing the test when the products are not average bioequivalent. But that is not the case here – the chance of passing if the geometric mean ratio is 1.0 is almost ten times (9.91 times, actually) higher than the chance of passing if the geometric mean ratio is 0.8 or 1.25. So even though the power of this study for AUC, based on the variance estimate obtained from the study, is poor in the absolute sense (less than a 50:50 chance of passing even if the geometric mean ratio is 1.0), it is still substantially more likely to pass if you are equivalent than it is if you are not equivalent. Therefore, I see no statistical basis to discount the successful test result.

As we discussed, there could possibly be *other* reasons for discounting the successful test result. For example, if you feel that the subjects whose data were deleted would, if they had been properly studied, have produced data that would have led to failing the bioequivalence test. Or if you feel that the problems found by Division of Scientific Investigations may be indicative of other unidentified problems, thus invalidating the study. I will leave those considerations to you.

Don Schuirmann
DB6/Office of Biostatistics

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

/s/

Carol Noory
12/12/2008 01:55:17 PM
BIOPHARMACEUTICS

Veneeta Tandon
12/12/2008 02:03:36 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Generic Name:	Lamotrigine
Brand Name:	Lamictal®
NDA:	22-251
Dosage Form:	Orally Disintegrating Tablets
Dosage Strengths:	25 mg, 50 mg, 100 mg, and 200 mg
Indication:	Treatment of Seizure Disorders
NDA type:	505(b)(1)
Submission Date(s):	November 28, 2007
Sponsor:	GlaxoSmithKline (GSK)
Related applications:	IND 43,551 (9/30/1993) and (b) (4)
Reviewer:	Carol Noory
Team Leader:	Ramana Uppoor, Ph.D.
OCP Division:	DCP-1, HFD-860
OND Division:	Neurology HFD-120

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I. EXECUTIVE SUMMARY

Lamictal® (Lamotrigine) is an anticonvulsant drug approved as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients. It is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug and for use in the maintenance treatment of bipolar I disorder to delay time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy. Lamictal® is currently marketed in the US as immediate-release (IR) compressed 25mg, 50mg, 100mg and 200mg Tablets (NDA 20-241) and 2mg, 5mg and 25mg Chewable Dispersible Tablets (NDA 20-764) both marketed by GlaxoSmithKline.

The current NDA seeks approval of Lamictal® 25 mg, 50 mg, 100 mg and 200 mg orally disintegrating tablets [ODT]. The ODT is designed to rapidly disintegrate in the mouth without chewing or water and offers an immediate release option for patients who have difficulty swallowing tablets. All relevant non-clinical and clinical safety and efficacy data for approved IR compressed tablet formulation and the chewable dispersible tablet formulation will be incorporated by reference.

The orally disintegrating tablet formulation was developed by Eurand Inc., Vandalia, Ohio. The formulation consists of Eurand's proprietary methods using technologies designed to mask the bitter taste of lamotrigine and achieve a desired dissolution profile (Microcap® and AdvaTab®). All four strengths are compositionally proportional to each other and are manufactured from one common blend, with different tablet weights.

In support of the application, the Sponsor has included a pilot study [LBI108614] using two prototype formulations versus the Lamictal® IR compressed tablet and a pivotal bioequivalence study using the to-be-marketed (TBM) formulation [LBI108617]. The formulation chosen from the preliminary study was used in the pivotal *in vivo* study, LBI108617, a four-arm parallel-group study designed to demonstrate the bioequivalence of the ODT to the Lamictal® IR tablet and to determine the effect of food and water on the ODT.

1. Summary of General Pharmacokinetic Characteristics of Lamotrigine from Study LBI108617:
    - The highest strength, 200 mg, lamotrigine ODT formulation was comparable relative to the currently approved Lamictal® 200 mg IR tablet for both AUC(0–∞) [91.0%] and Cmax [94.1%], the 90% CI of the ratio lamotrigine 200 mg ODT: IR were within the equivalence range of 80.0% to 125.0%.
    - The relative bioavailability of the highest strength ODT when dosed with a high fat meal was similar to the ODT dosed in the fasted state. There was no effect of food on lamotrigine 200 mg ODT for AUC(0–∞). For Cmax, the lower limit of the 90% confidence interval of the ratio of lamotrigine 200 mg ODT, fed: fasted was slightly lower (78.9%) than the lower limit of the acceptance range.
    - Lack of effect of swallowing the lamotrigine ODT whole with water was demonstrated both for AUC(0–∞) and Cmax, compared with allowing the tablet to disintegrate in the mouth
    - An organoleptic questionnaire indicated that subjects who had received the ODT were generally satisfied with the time to disintegration, flavor, strength of flavor, mouth feel and aftertaste.
    - According to the sponsor, safety of the ODT is similar to the conventional IR tablet.

Labeling:

1. Labeling to include the orally disintegrating tablet was submitted. In support of the proposed label claim that lamotrigine ODT formulation can be given without regards to food and water effects, Study LBI108617 demonstrated that there was no effect on the extent of lamotrigine absorption from the 200 mg ODT formulation, in the presence or absence of a high-fat meal, and with or without administration with water.
2. With regards to food, the Lamictal® IR tablet label states: "The bioavailability is not affected by food." This is acceptable for the ODT also. A minor change has been recommended with regards to administration with or without food. In section 2.6, of the label "ADMINISTRATION OF LAMICTAL ODT ORALLY DISINTEGRATING TABLETS", the sponsor has stated that (b) (4)

   The last sentence should be revised to state that: "The tablet will disintegrate rapidly, can be swallowed with or without water, and can be taken with or without food."

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 has reviewed NDA 22-251 and finds the Clinical Pharmacology section of the application acceptable

pending the results of the DSI inspection and provided that the labeling recommendations proposed by the reviewer (**1.2 Comments to be forwarded to the Sponsor**) below are acceptable to the sponsor.

1.2 Comments to be forwarded to the Sponsor

In section 2.6, of the label "ADMINISTRATION OF LAMICTAL ODT ORALLY DISINTEGRATING TABLETS", the sponsor has stated that (b) (4) The last sentence should be revised to state that: "The tablet will disintegrate rapidly, can be swallowed with or without water, and can be taken with or without food."

1.3 Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

This NDA is submitted in accordance with section 505b(1) of the Federal Food, Drug and Cosmetic Act, referencing the safety and efficacy information for Lamictal® immediate-release (IR) tablets (NDA 20-241) approved December 27, 1994 and Lamictal® Chewable Dispersible Tablets (NDA 20-764) approved August 24, 1998. The sponsor selected an ODT formulation to develop by conducting a bioavailability study (LBI108614) to evaluate the pharmacokinetic characteristics of two prototype formulations of 25 mg and 200 mg lamotrigine ODT versus the immediate release lamotrigine tablet. The basis for approval of this application is data from the pivotal bioequivalence study (LBI108617) comparing the ODT formulation to the approved Lamictal® IR tablet formulation. This study also investigated the effect of food and water on the bioavailability of the ODT formulation.

The Office of Clinical Pharmacology has reviewed the following information submitted:

1. **Study LBI108617:** An open-label, randomized, single-dose, four-arm parallel group study to demonstrate bioequivalence of two formulations and the effect of food and water on one formulation of lamotrigine in healthy male and female volunteers.

The results of this study determined:

- **Bioequivalence to Lamictal IR Tablets:**
  Bioequivalence of the lamotrigine 200 mg ODT formulation was established relative to the currently approved Lamictal® 200 mg IR tablet. For both AUC(0–∞) [91.0%] and Cmax [94.1%], the 90% CI of the ratio lamotrigine 200 mg ODT: IR, fasted were within the equivalence range of 0.800 to 1.250 indicating bioequivalence of lamotrigine 200 mg ODT to the IR tablet.

- **Effect of Food**:
  The highest strength ODT when dosed with a high-fat meal showed comparable exposure to the ODT dosed in the fasted state. When dosed with food, the 90% CI of the ratio of AUC (0-∞) (lamotrigine 200 mg ODT fed: fasted) was within the equivalence range 0.800 to 1.250 indicating no effect of food on AUC(0–∞). However, for Cmax [mean 84.3%], the lower limit of the 90% CI of the ratio lamotrigine 200 mg ODT, fed: fasted was slightly lower than the limit (78.9%-90.1%).

- **Effect of Dosing without Water**:
  Lack of effect of swallowing the lamotrigine ODT whole with water was demonstrated both for AUC(0–∞) and Cmax, compared with allowing the tablet to disintegrate in the mouth.

  For both AUC(0–∞) [104.1%] and Cmax [100.5%], the 90% CI of the ratio lamotrigine 200 mg ODT, fasted, with water: lamotrigine 200 mg ODT fasted, without water were inside the equivalence range 0.800 to 1.250 indicating lack of effect of water on lamotrigine 200 mg ODT.

- **Organoleptic Data**: An organoleptic questionnaire indicated that subjects who had received the ODT were generally satisfied with the time to disintegration, flavor, strength of flavor, mouth feel and aftertaste.

- **Safety:** According to the sponsor, the safety and tolerability of the ODT is similar to the Lamictal® IR tablet (fasted state).

2. **Study LBI108614:** An open-label, randomized, single-dose, parallel-group study to evaluate the pharmacokinetic characteristics, safety and tolerability of up to two formulations (with different taste-masking approaches) of an orally disintegrating tablet (ODT) of lamotrigine at 25mg and 200mg versus the immediate-release (IR) lamotrigine in healthy subjects. The results of this study determined:
   a. At corresponding doses, lamotrigine systemic exposure (based on Cmax and AUC) was similar for both the lamotrigine ODT and IR formulations in the fasted state.
   b. The half life of lamotrigine was similar for lamotrigine ODT and IR formulations and across different dosage strengths, being approximately 35 hours.
   c. Following Part A of the study (taste-masking approach 1: microencapsulation), comparable PK data for the ODT and commercial IR formulations was shown and a decision not to proceed with Part B (taste-masking approach 2: granulation) was made.
   d. Both dosage strengths and formulations were well tolerated. There were no new safety issues following dosing with the ODT formulation.

e. The ODT formulation was considered pleasant and easy to take.

3. **Labeling:**
   The proposed labeling for this NDA is a single combined label for Lamictal® ODT, IR and Chewable formulations. In addition to the revisions resulting from the NDA itself, the proposed labeling for LAMICTAL has been further revised to comply with the January 24, 2006 Final Rule *"Requirements on Content and Format of Labeling for Prescription Drug and Biological Products"*.

4. **Request for Waiver of Pediatric Studies:** Pursuant to 21 CFR 314.55 (c)(3), GlaxoSmithKline (GSK) requests a waiver for conducting clinical studies in pediatric patients with Lamictal® ODT. In an October 1, 2007 meeting, DNP and DPP agreed that, given that Lamictal ODT is likely to be used for some patients in the pediatric age range, a deferral of pediatric studies rather than a waiver would be granted.

Site Inspection:
At the request of DCP1, on February 4, 2008, the Division of Neurology Products requested an inspection of the following studies/sites pivotal to approval:

Study #	**Clinical Site (name, address, phone, fax, contact person, if available)**	**Analytical Site (name, address, phone, fax, contact person, if available)**
Study LBI-108617	**Clinical:** Convance Clinical Research Unit 1341 West Mockingbird Lane Suite 400 Dallas, Texas 75247	**Analytical:** **WorldWide Bioanalysis** Drug Metabolism and Pharmacokinetics GlaxoSmithKline R&D; 3030 Cornwallis Road, RTP, NC 27709

The DSI inspection is still pending.

1.4. Signatures

Reviewer: Carol Noory

Team Leader: Ramana Uppoor

cc list:

DFS: NDA 22-251
HFD-860: (NooryC, UppoorR, MehtaM)

HFD-120: (KatzR, WareJ, SheridanP, HershkowitzN)

II. Question Based Review

2.1. General Attributes of the Drug

2.1.1. What pertinent regulatory background or history contributes to the current assessments of this drug?

GlaxoSmithKline, the sponsor of this NDA, is the current holder of NDA 20-241 for Lamictal® IR tablets and NDA 20-764 for Lamictal® Chewable Dispersible Tablets. All information for the lamotrigine drug substance is incorporated by cross-reference to approved NDA 20-241 for Lamictal® conventional tablets.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs.

Other name: GI267119

Solubility: Lamotrigine is slightly soluble in water (0.17 mg/mL at 25^{o} C). It has a pKa of 5.7.

Dosage Form and Strength:

Lamictal® Orally Disintegrating Tablets (ODT) are for oral administration. The tablets contain 25 mg (white to off-white), 50 mg (white to off-white), 100 mg (white to off white), or 200 mg (white to off-white) of lamotrigine and the following inactive ingredients:

- artificial cherry flavor, crospovidone, ethylcellulose, mannitol, and sucralose.

Lamictal® ODT are formulated using technologies (Microcaps®* and AdvaTab®*) designed to mask the bitter taste of lamotrigine and achieve a rapid dissolution profile.

Indication:

LAMICTAL is approved as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients. It is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital,

primidone, or valproate as the single antiepileptic drug. LAMICTAL is also approved for use in the maintenance treatment of bipolar I disorder to delay time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy.

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have not been established.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

Lamictal® Orally Disintegrating Tablets, available in 20, 50, 100 and 200 mg strengths, are intended to be administered orally by being placed on the tongue, allowed to disintegrate and subsequently swallowed with or without water.

2.2. General Clinical Pharmacology

The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure.

2.2.1. What are the design features of the Clinical Pharmacology and Clinical Studies used to Support the Dosing or Claims?

The pivotal clinical pharmacology study (LBI108617) was designed to demonstrate the bioequivalence of the highest strength of the Lamictal® ODT to the equivalent strength of the Reference product, Lamictal® conventional IR tablet. By demonstrating bioequivalence, the ODT is able to use the Agency's finding of efficacy and safety determined for the reference IR tablet. The study also determined the effect of dosing the ODT with a high fat meal (Effect of Food) and the effect of dosing the ODT without water on the bioavailability.

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

Yes, the parent compound was measured using a validated bioanalytical method.

2.2.3. Does Lamotrigine affect the QT or QTc interval?

Full 12-lead ECGs were used to automatically calculate the heart rate and measure PR, QRS, QT and QTc intervals. The sponsor reported that there was a trend for a slight reduction in QTc(B) following dosing (median value at 24 hours of -1.5 to -7.5 msec).

2.3. Pharmacokinetic Characteristics

2.3.1. What are the single-dose pharmacokinetic characteristics of the drug?

In the current application, reference is made to the basic pharmacokinetic and metabolism information on lamotrigine available in the literature and in the approved labeling for Lamictal® IR tablet and Chewable tablet. According to the reference label, the pharmacokinetics of lamotrigine following a single and multiple-dose are linear with a long half-life and low protein binding (55%). In the current submission, a single dose of the ODT was compared to a single dose of the marketed IR tablet in a parallel study (LBI108617). The results are shown in the following table:

Table 1: Single Dose Pharmacokinetics of Lamotrigine

Treatment regimen	N	AUC(0–∞) (μg.h/mL)[1]	AUC(0–t) (μg.h/mL)[1]	Cmax (μg/mL)[1]	tmax (h)[2]	t½ (h)[1]	tlag (h)[2]
C	54	161 (43.4)	147 (35.0)	3.44 (20.0)	1.59 (0.50–4.07)	37.2 (40.4)	0.00 (0.0–0.3)
D	54	177 (37.4)	158 (30.6)	3.65 (22.0)	1.00 (0.50–12.00)	39.1 (34.9)	0.00 (0.0–0.5)
E	54	160 (44.9)	146 (36.5)	2.90 (19.3)	4.04 (1.00-10.02)	36.5 (34.8)	0.00 (0.0–0.8)
F	53	168 (38.0)	152 (30.8)	3.46 (22.9)	2.00 (0.75–8.00)	36.0 (35.8)	0.00 (0.0–0.0)
G	1	168	152	2.65	4.05	40.2	0.00

Source Data: Table 11.1 and Table 11.2
AUC(0–∞) = Area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time, AUC(0–t) = Area under the serum concentration-time curve from zero (pre-dose) to time of last quantifiable concentration, Cmax = Maximum observed serum concentration, tmax = Time to maximum observed serum concentration, t½ = Apparent terminal elimination half-life, tlag = lag time;
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted
Regimen G: 200mg ODT swallowed with water/fed
1. Geometric mean (Coefficient of variation)
2. Median (Range)

2.3.2 General ADME Characteristics of the Drug

After lamotrigine is absorbed it is expected to have the same distribution, protein binding, metabolism, and elimination as the currently approved formulations. The key ADME characteristics are taken from the FDA Approved Labeling Text for Lamictal® IR Tablets and from Lamictal® Chewable Dispersible Tablet. The following comments can be made based on single-dose pharmacokinetics of Lamictal® ODT and the current Lamictal IR label:

Absorption: 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 anywhere from 1.4 to 4.8 hours following drug administration (0.5-4 hours for the ODT). The lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets swallowed with water.

2.3.3 What is the inter-subject variability in PK parameters?

In the current submission, the pooled between-subject CV from the statistical analyses were 41.0% and 21.1% for AUC(0-inf) and Cmax respectively. A summary of the between-subject CV for primary pharmacokinetic parameters is presented in the following table.

Table 2: Summary of Between-Subject Coefficient of Variation for Primary PK parameters

Parameter	Regimen C	Regimen D	Regimen E	Regimen F
AUC(0–∞)	43.44	37.37	44.88	37.94
Cmax	20.035	21.991	19.333	22.866

Source Data: Table 11.2
AUC(0–∞) = Area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time, Cmax = Maximum observed serum concentration;
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted

2.4. General Biopharmaceutics

The Biopharmaceutics program was designed to address the performance of the proposed ODT formulation compared to the approved IR tablet reference product and the effect of taking the ODT with water and with food.

2.4.1. What is the proposed formulation of the drug product?

Table 3 provides the quantitative compositions for Lamotrigine ODT. The commercial formulation is identical to the formulation used in the pivotal pharmacokinetic study.

Table 3: Composition of Lamotrigine Orally Disintegrating Tablets

Ingredient	mg/tablet			
	25 mg	50 mg	100 mg	200 mg
Lamotrigine	25.00	50.00	100.00	200.00
Mannitol (b) (4)	(b) (4)			
Ethylcellulose NF				
Crospovidone NF				
Artificial Cherry Flavor (b) (4) (b) (4)				
Sucralose NF				
Total				

Magnesium stearate NF (b) (4) is used (b) (4) (b) (4)

All four strengths are dose-proportional to each other and are manufactured from one common blend, with different tablet weights.

No overages are added to this formulation.

2.4.2. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The proposed to-be-marketed formulation is identical to the formulation used in the pivotal pharmacokinetic study.

2.4.3. Are the lower strengths, 25 mg, 50 mg and 100 mg ODT proportionately similar to the highest 200 mg strength?

All strengths of the ODT are made from a single blend and are compositionally proportional. A biowaiver for the 25, 50 and 100 mg strengths is requested and will be reviewed by ONDQA.

2.4.4. Is the to-be-marketed ODT formulation bioequivalent to the RLD formulation of same strength?

Yes, the bioequivalence of the ODT formulation was established in a single-dose, four-arm parallel study (Study LBI108617) conducted in 216 healthy male and female volunteers. The highest strength, 200 mg, lamotrigine ODT formulation was bioequivalent under fasted conditions relative to the currently approved lamotrigine 200 mg IR tablet for both AUC(0–∞) [91.0%] and Cmax [94.1%], the 90% CI of the ratio lamotrigine 200 mg ODT: IR were within the equivalence range of 80.0% to 125.0%;

2.4.5. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The current label for the IR tablet states that the bioavailability is not affected by food. The current study showed there was no effect of food on lamotrigine 200 mg ODT for AUC(0–∞). For Cmax, the lower limit of the 90% confidence interval of the ratio lamotrigine 200 mg ODT, fed: fasted was slightly lower (78.9%) than the lower limit of the acceptance range. Since the exposure is similar for the ODT with or without food, the ODT can be dosed without regard to food.

2.4.6. What is the effect of dosing the ODT with water on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to dosing with water?

The ODT can be dosed with or without water. Study LBI108617 demonstrated the lack of effect when the ODT dosed with water was compared to the ODT dosed without water allowing the tablet to disintegrate in the mouth. For both AUC(0–∞)[104.1%] and Cmax [100.5%], the 90% CI of the ratio of lamotrigine 200 mg ODT, fasted, with water: lamotrigine 200 mg ODT fasted, without water were inside the equivalence range 0.800 to 1.250 indicating lack of effect of water on lamotrigine 200 mg ODT.

2.5 Literature

The sponsor conducted a literature search as requested by FDA.

2.6. Analytical

2.6.1. Were the correct moieties identified and properly measured?

Yes, the parent compound was measured.

2.6.2. What bioanalytical methods are used to assess concentrations?

The method for the determination of lamotrigine (GI267119) in human serum was an HPLC-MS/MS. Lamotrigine was extracted from 25 µL of human serum by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([$^{15}N_5{}^{13}C_2$] –GI267119). Extracts are analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring.

2.6.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The HPLC-MS/MS method was validated over the range 10 to 10000 ng/mL. The pivotal study Cmax was approximately 4µg/mL (4000 ng/mL). The regression model used peak area ratios with $1/x^2$ weighted linear regression.

2.6.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
The method is validated between 10 ng/mL and 10000 ng/mL.

2.6.5 What are the accuracy, precision, and selectivity at these limits?
Calibration standards were used to establish the linearity of the method over the concentration range of 10 to 10000 ng/mL GI267119 in human serum. Table 5 shows the accuracy and precision of QC samples over this range.

Table 4: Overall Statistics: Bias, Precision for GI267119 in Human Serum

	GI267119 (Serum) ng/mL				
	10.0	30.0	800.0	8000.0	10000.0
Mean (ng/mL)	10.5	31.5	815.1	7644.3	10005.2
S.D.	1.0	2.8	45.9	630.8	522.7
Precision (%)	9.0	8.8	5.6	8.3	5.2
Bias (%)	5.5	4.9	1.9	-4.4	0.1
N	24	24	24	24	24
Avg. within run Precision	7.2	8.4	2.7	3.0	2.5
Between Run Precision	6.3	3.0	5.6	8.7	5.2

The selectivity of the method was established by the analysis of samples of control human serum from 6 individual volunteers. Blank and double blank samples were prepared from control human serum in validation assays. HPLC-MS/MS chromatograms of the blanks and validation samples were visually examined and compared for chromatographic integrity and potential interferences. Representative chromatograms of a double blank sample, blank sample and validation samples at the LLQ and HLQ showed no unacceptable interferences at the retention times of GI267119 and its internal standard.

2.6.6 What is the sample stability under the conditions used in the study?
The stability of GI267119 in spiked human serum samples stored at room temperature was assessed at 30 and 8000 ng/mL (in replicates of 6) by comparing the mean concentrations of samples extracted after storage for 24 hours against those of the samples extracted immediately upon spiking. The difference is less than 15%, and indicates that GI267119 is stable in human serum stored at room temperature for at least 24 hours.

2.6.7 What is the QC sample plan?

The Quality Control Rejection Criteria allowed the individual QC results if the calculated concentration deviated by no more than 15% from the actual concentration. The analytical run was approved if no more than one-third of the QC results exceeded the acceptable limit and at least 50% of the results at each concentration were within the acceptable limit.

III. Detailed Labeling Recommendations

The sponsor's proposed labeling incorporates the ODT information into the approved labeling for the IR tablet and the Chewable Tablet. The format of the labeling was rewritten to conform to the PLR labeling format.

Comment:

The sponsor's proposed labeling was compared to the recommended labeling for the XR tablets (N22 115; approvable letter with recommended labeling revisions 9/20/2007) and to the approved IR/chewable tablet labeling. The Dose and Administration (Section 2); Drug Interaction Section (Section 7); Use in Specific Populations (Section 8); and the Clinical Pharmacology Section of the label are acceptable as proposed with a minor change to section 2.6. In section 2.6, of the label "ADMINISTRATION OF LAMICTAL ODT ORALLY DISINTEGRATING TABLETS", (b) (4) (b) (4) (b) (4) The last sentence should be revised to state that: "The tablet will disintegrate rapidly, can be swallowed with or without water, and can be taken with or without food." The sponsor's proposed labeling is attached (V. SPONSOR'S PROPOSED LABELING).

IV. INDIVIDUAL STUDY REVIEWS

4.1. Study LBI108617(Pivotal Study)

Study LBI108617

(Lamotrigine, orally disintegrating tablet, bioequivalence, food effect, water effect, pharmacokinetics, in healthy subjects, GI267119)

Title:
An open-label, randomized, single-dose, parallel-group study to demonstrate bioequivalence of two formulations and the effect of food and water on one formulation of lamotrigine in healthy male and female volunteers.

Phase: I
Compound Number: Lamotrigine **(**GI267119)

Study Dates: 03-May-2007 -19-Jun-2007
Date of Report: September 2007

Primary Investigator:	**Dr. P.A. Chandler**
Site:	**Covance Clinical Research Unit**
	1341 West Mockingbird Land, Suite 400 E
	Dallas, Texas 75247

OBJECTIVES

Primary Objectives

- To demonstrate bioequivalence of the 200 mg ODT lamotrigine formulation relative to the reference 200 mg immediate release tablets (IR) in the fasted state.
- To demonstrate lack of effect of food on the pharmacokinetics of the 200 mg ODT lamotrigine formulation.
- To demonstrate lack of effect of administration with water on the pharmacokinetics of the 200 mg ODT lamotrigine formulation.

Secondary Objectives

- To evaluate the safety and tolerability of a single dose of the 200 mg ODT lamotrigine formulation administered under fasted and fed states, and administered with water in healthy male and female volunteers.
- To collect organoleptic questionnaire data.

STUDY DESIGN

This was an open-label, randomized, single-dose, parallel-group study to demonstrate bioequivalence of oral disintegrating tablet (ODT) and immediate release tablet (IR) formulations

of lamotrigine and the effect of food and water on the ODT formulation of lamotrigine in healthy male and female volunteers. A parallel group design was selected to avoid repeated administration of single doses of lamotrigine to healthy subjects due to possible increase in the risk of skin rash. Based on the highest between-subject CV observed in other lamotrigine trials (32.7% and 20.4%) for AUC(0–∞) and Cmax, respectively, it was determined that a sample size of 50 evaluable subjects per arm would have a power of over 90% to demonstrate bioequivalence or lack of food and water effects for either primary pharmacokinetic parameter, if the true ratio of the geometric means of the test and reference treatments was equal to one.

Products:

TEST: Lamotrigine 200 mg ODT (Lot number: PF398EA0004; (b) (4) manufactured 1/29/2007; cherry-flavored tablets)

REFERENCE: Lamotrigine 200 mg IR tablets (batch number: 7ZP6825)

Treatments:

Four Treatment Arms:

- Regimen C: Lamotrigine 200 mg ODT, administered following a fast of at least 10 hours and allowed to disintegrate in the mouth without water.
- Regimen D: Lamotrigine 200 mg REFERENCE, administered with 240 mL of water following a fast of at least 10 hours.
- Regimen E: Lamotrigine 200 mg ODT, administered after an FDA high-fat meal and allowed to disintegrate in the mouth without water.
- Regimen F: Lamotrigine 200 mg ODT, administered with 240 mL of water following a fast of at least 10 hours.

An unplanned fifth arm was created as one subject, randomized to Regimen F, received breakfast in error instead of fasting. The treatment was thus assigned as follows:

Regimen G: Lamotrigine 200 mg ODT, administered after an FDA high-fat meal with water. This subject was excluded from the statistical analysis but included in the summary statistics. Subjects were dosed following an overnight stay in the unit.

Subjects:

55 subjects were recruited in each arm in order to obtain 50 evaluable subjects in each arm. A summary of the disposition of subjects is presented in Table 1.

Table 1: Subject Disposition

Number of subjects	Regimen C	Regimen D	Regimen E	Regimen F	Regimen G	Total
Planned	55	55	55	55	0	220
Randomised	54	54	54	54	0	216
Treated	54	54	54	53	1	216
Completed n (%)	53 (98)	54 (100)	53 (98)	52 (98)	1 (100)	213 (99)
Total withdrawn (any reason), n (%)	1 (2)	0	1 (2)	1 (2)	0	3 (1)
Withdrawn due to adverse events, n (%)	0	0	0	0	0	0

Source Data: Table 9.5

Demographic characteristics were generally similar across all regimens for age, height, weight and body mass index. Regimen C had a lower percentage of females compared with Regimens D-F (39% versus 48–55%). Regimen F had a higher percentage of subjects of Hispanic and Latino ethnicity compared with Regimens C-E (45% versus 30– 37%). The demographic characteristics of the treatment groups are presented in Table 2.

Table 2: Subject Demographics

Characteristic	Regimen C	Regimen D	Regimen E	Regimen F	Regimen G[1]	Total
n	54	54	54	53	1	216
Age (years)						
Median (range):	36.0 (19–52)	33.0 (19–54)	32.0 (19–53)	36.0 (20–55)	42.0 (42–42)	34.0 (19–55)
Sex						
Female n (%):	21 (39)	26 (48)	28 (52)	29 (55)	1 (100)	105 (49)
Male n (%):	33 (61)	28 (52)	26 (48)	24 (45)	0	111 (51)
Ethnicity						
Hispanic or Latino n (%):	17 (31)	20 (37)	16 (30)	24 (45)	0	77 (36)
Not Hispanic or Latino n (%):	37 (69)	34 (63)	38 (70)	29 (55)	1 (100)	139 (64)
Race						
African American / African heritage n (%)	21 (39)	17 (31)	21 (39)	16 (30)	1 (100)	76 (35)
American Indian or Alaska Native n (%)	1 (2)	1 (2)	0	0	0	2 (<1)
Asian – Central/ South Asian heritage n (%)	0	0	0	1 (2)	0	1 (<1)
Native Hawaiian or other Pacific Islander n (%)	1 (2)	0	0	0	0	1 (<1)
White – Arabic/ North African heritage n (%)	2 (4)	2 (4)	2 (4)	2 (4)	0	8 (4)
White – White /Caucasian/ European heritage n (%)	29 (54)	34 (63)	31 (57)	33 (62)	0	127 (59)
Mixed race n (%)	0	0	0	1 (2)	0	1 (<1)
Height (cm)						
Median (range):	171.0 (153–188)	168.5 (147–193)	166.5 (137–200)	166.0 (149–195)	173.0 (173–173)	168.0 (137–200)
Weight (kg)						
Median (range):	72.7 (50–99)	74.7 (47–118)	70.9 (47–126)	72.3 (54–110)	79.3 (79–79)	73.0 (47–126)
Body mass index (kg/m^2)						
Median (range):	25.54 (19.6–31.6)	26.44 (19.6–32.0)	26.13 (19.8–31.7)	26.02 (20.6–31.6)	26.50 (26.5–26.5)	26.04 (19.6–32.0)

Source Data: Table 9.1
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted
1. Subject 336 was randomised to Regimen F but received breakfast in error, instead of fasting. This subject was thus assigned as Regimen G as actual treatment and for purposes of reporting.

Sample Collection

Blood samples were collected from each subject at pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose. Serum samples were frozen at -20°C ± 10°C until assayed by a validated LC-MS/MS method.

BIOANALYTICAL ASSAY METHOD

Lamotrigine was extracted from human serum by protein precipitation using acetonitrile containing [$^{15}N_5{}^{13}C_2$] -Lamotrigine as an internal standard. Extracts were analyzed by HPLC-MS/MS using a TurboIonspray™ interface with positive ion multiple reaction monitoring. A five-point calibration curve was used to establish the linearity of the method. Each batch of experimental samples was run against duplicate freshly prepared calibration standards (n = 7). QC samples at three concentrations (2 replicates per concentration), were also included in the run to establish the bias and precision of the method. A summary of the method performance is given in Table 3:

Table 3: Bioanalytical Method Parameters		
Bioanalytical Method Performance		
Matrix		Serum
Method		LC-MS-MS
Sample Size		25 µL aliquot
Calibration Standards		
Calibration Standards	Range	10, 20, 100, 200, 1000, 2000, 10000 ng/mL
	Date of Analysis	June 6-25, 2007
	Slope (n=)	0.001482
	Linearity	0.997585
n=143-150	Interday Precison (%CV)	3.8-8.3%
	Interday Accuracy (%RE)	96.6-101.9%
LOQ n=143	Concentration	10 ng/mL
	Precision	7.6%
	Accuracy	100.6%
ULOQ n=149	Concentration	10000 ng/mL
	Precision	4.2%
	Accuracy	101.9%
Quality Control Samples		
Low-30 ng/mL	Precision	11.7%

n=147	Accuracy	5.0%
Medium-800 ng/mL	Precision	5.3%
n=150	Accuracy	2.4%
High-8000 ng/mL	Precision	5.0%
n=150	Accuracy	5.2%

The pharmaceutical repeats were acceptable.

STUDY ASSESSMENT PROCEDURES AND RESULTS

Safety Assessments:
Safety assessments were conducted at screening and during the study and included physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, and urinalysis for drugs of abuse, nicotine and alcohol). In addition, pregnancy tests were performed on all female subjects.

Adverse events were monitored throughout the study. Subjects were not permitted to take any medication (with the exception of acute use of ibuprofen), restrictions were made regarding strenuous activity, alcohol, smoking, caffeine and certain foods/drinks suspected to inhibit or induce the synthesis of metabolic phase-1 enzymes (cytochrome P450 enzyme activity) and phase-2 enzymes (conjugating enzymes i.e., glucuronidases, sulphatases).

Two hundred and sixteen subjects were included in the safety assessment (subjects who received at least one dose of study drug). Safety data was reviewed to identify a range of values which were of potential clinical concern (PCC). Standard PCC ranges were used for clinical laboratory (haematology), clinical chemistry, ECGs and vital signs.

A summary of the most frequently reported TEAEs (>1 subject in the entire study) during the study is presented in Table 4.

Table 4: Summary of the most frequently reported (>1 subject in the entire study) treatment emergent adverse events during the study (Safety Population)

Preferred term	Regimen C N = 54 n (%)	Regimen D N = 54 n (%)	Regimen E N = 54 n (%)	Regimen F N = 53 n (%)	Regimen G[1] N = 1 n (%)
Any event	14 (26)	13 (24)	15 (28)	18 (34)	0
Headache	5 (9)	4 (7)	10 (19)	3 (6)	0
Diarrhoea	3 (6)	0	1 (2)	2 (4)	0
Nausea	2 (4)	2 (4)	1 (2)	1 (2)	0
Vessel puncture site pain	1 (2)	1 (2)	1 (2)	1 (2)	0
Pain in extremity	0	1 (2)	1 (2)	1 (2)	0
Rhinitis allergic	0	0	1 (2)	2 (4)	0
Contusion	1 (2)	0	0	1 (2)	0
Cough	0	0	0	2 (4)	0
Dry mouth	0	0	1 (2)	1 (2)	0
Pleuritic pain	1 (2)	1 (2)	0	0	0
Presyncope	1 (2)	1 (2)	0	0	0
Somnolence	0	0	1 (2)	1 (2)	0
Upper respiratory tract infection	0	0	2 (4)	0	0
Vision blurred	0	1 (2)	0	1 (2)	0
Vomiting	0	1 (2)	0	1 (2)	0

Source Data: Table 10.2
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted
1. Subject 336 was randomised to Regimen F but received breakfast in error, instead of fasting. This subject was thus assigned as Regimen G as actual treatment and for purposes of reporting.

ORGANOLEPTIC ASSESSMENT

Subjects were given a questionnaire and were asked to rate the answers to each question on a scale of 1 to 5. Only subjects in Regimen C (ODT Fasted/ Disintegrate in the mouth without water), Regimen D (IR Fasted/ Swallow with water) and Regimen E (ODT Fed/ Disintegrate in the mouth without water) were given the questionnaires. The results for both fasted and fed ODT regimens were similar in acceptability. Most subjects in both regimens appeared to find the ODT tablet pleasant to taste and convenient to take in comparison to standard tablets that are taken with water.

PHARMACOGENETIC ASSESSMENTS

Approximately 10 mL of blood was collected from subjects taking part in the pharmacogenetics research. The samples were frozen at -20°C prior to shipment to (b) (4) for storage and possible future analysis. Eighty-six percent of subjects in this study consented to provide a blood sample for pharmacogenetic research. Samples were collected from 81% of subjects.

PHARMACOKINETIC ASSESSMENT

Pharmacokinetic analyses of serum lamotrigine concentration-time data were conducted using non-compartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 4.0.1. Actual elapsed time from dosing was used to estimate all individual serum pharmacokinetic parameters for evaluable subjects. Values for the following pharmacokinetic parameters were estimated following administration of a single-dose of lamotrigine.

- The Cmax, tmax and tlag were the actual observed values.
- Where possible, λz was estimated from log-linear regression analysis of the terminal phase of the serum concentration-time profile. The t½ was calculated as t½ = ln2/λz.
- The AUC(0-t) and AUC(0-∞) were calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method was used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations. The percentage of AUC(0-∞) obtained by extrapolation (%AUCex) was calculated as ((AUC(0-∞) - AUC(0-t))/ AUC(0-∞)) * 100.

STATISTICAL ANALYSIS

- The statistical analysis of derived pharmacokinetic parameters from serum lamotrigine concentration-time data was analyzed SAS, Version 8. For each of these parameters, except tmax, the following summary statistics were calculated and tabulated by treatment: n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, standard deviation (SD), minimum, median, maximum, geometric mean, 95% confidence interval for the geometric mean and SD of loge-transformed data.
- For tmax, median, minimum, maximum, arithmetic mean, 95% CI for the arithmetic means, SD and CV were calculated.
- Between subject coefficients of variation were calculated according to two methods:
    - Method 1 = 100*(SD/Mean). This method was used in the summary statistics of log-transformed derived serum lamotrigine pharmacokinetic parameters.
    - Method 2 = 100*(sqrt(exp(SD of loge-transformed)2-1)). This method was used in Summary of statistical analysis of primary endpoints for bioequivalence of lamotrigine ODT 200 mg compared with IR.

PHARMACOKINETIC RESULTS

Point estimates and corresponding 90% CIs were constructed for the primary assessments of interest of 200 mg bioequivalence (Regimen C:Regimen D), 200 mg ODT food effect (Regimen E: Regimen C) and 200 mg ODT water effect (Regimen F:Regimen C) using the residual variance. These were then back-transformed to provide point estimates and corresponding 90% CIs for the geometric mean ratios C:D, E:C and F:C. Bioequivalence of 200 mg ODT to IR was to be concluded if the 90% CI for the geometric mean ratios (C:D) of AUC(0–∞) and Cmax were each completely contained within the range (0.8000, 1.2500).

As a secondary analysis, AUC(0–t) and t½ of lamotrigine had the same statistical analysis models applied as described for the primary endpoints but the resulting CIs for geometric mean ratios were not subject to having to meet the bioequivalence criteria of (0.8000, 1.2500) which the primary endpoints did.

The summary statistics of derived and log-transformed derived serum lamotrigine pharmacokinetic parameters are presented in Table 5.

Table 5: Summary of Selected Lamotrigine Pharmacokinetic Parameters

Treatment regimen	N	AUC(0–∞) (µg.h/mL)[1]	AUC(0–t) (µg.h/mL)[1]	Cmax (µg/mL)[1]	tmax (h)[2]	t½ (h)[1]	tlag (h)[2]
C	54	161 (43.4)	147 (35.0)	3.44 (20.0)	1.59 (0.50–4.07)	37.2 (40.4)	0.00 (0.0–0.3)
D	54	177 (37.4)	158 (30.6)	3.65 (22.0)	1.00 (0.50–12.00)	39.1 (34.9)	0.00 (0.0–0.5)
E	54	160 (44.9)	146 (36.5)	2.90 (19.3)	4.04 (1.00-10.02)	36.5 (34.8)	0.00 (0.0–0.8)
F	53	168 (38.0)	152 (30.8)	3.46 (22.9)	2.00 (0.75–8.00)	36.0 (35.8)	0.00 (0.0–0.0)
G	1	168	152	2.65	4.05	40.2	0.00

Source Data: Table 11.1 and Table 11.2
AUC(0–∞) = Area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time, AUC(0–t) = Area under the serum concentration-time curve from zero (pre-dose) to time of last quantifiable concentration, Cmax = Maximum observed serum concentration, tmax = Time to maximum observed serum concentration, t½ = Apparent terminal elimination half-life, tlag = lag time;
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted
Regimen G: 200mg ODT swallowed with water/fed
1. Geometric mean (Coefficient of variation)
2. Median (Range)

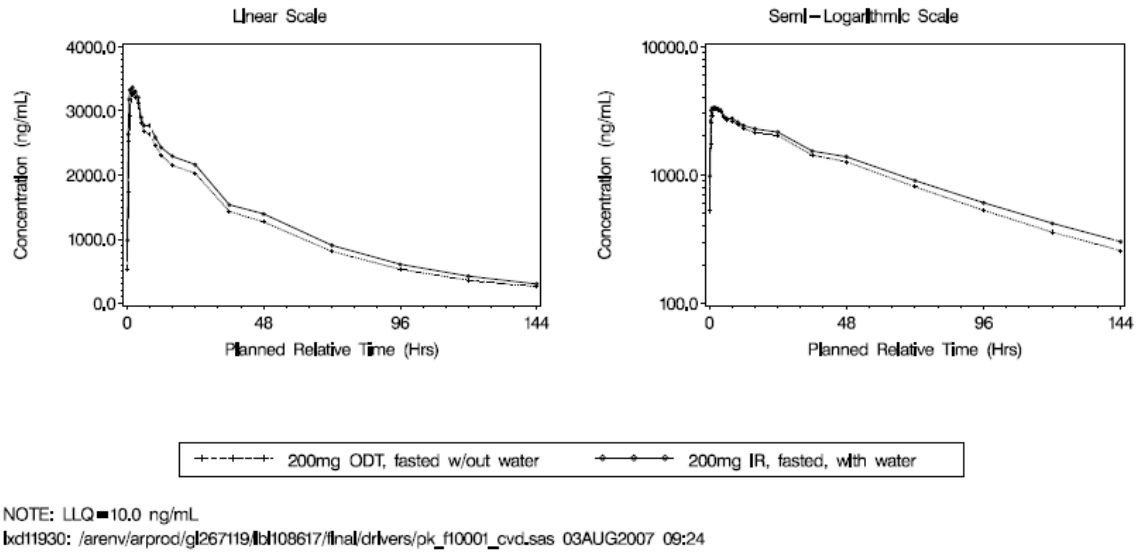
Percentages of AUC extrapolated to infinity were generally between 1% and 38% for all profiles and <20% subjects had %AUCex of >20%.

Bioequivalence of Lamotrigine 200 mg Oral Disintegrating Tablet to Lamotrigine 200 mg Immediate Release Tablet was determined for both AUC(0–∞) and Cmax. The 90% CI of the ratio lamotrigine 200 mg ODT: IR, fasted were inside the equivalence range of 0.800 to 1.250 indicating bioequivalence of lamotrigine 200 mg ODT to IR. A summary of the statistical results is presented in Table 6.

Table 6: Test of Bioequivalence between 200 mg ODT and 200 mg IR Tablet	
Ratio of Geometric Least Square Means (90% Confidence Interval)	
Parameter	Bioequivalence of lamotrigine 200 mg ODT to lamotrigine 200 mg IR Tablet (Treatment C:D)
AUC (0-inf)	0.910 (0.803, 1.031)
Cmax	0.941 (0.881, 1.006)

Linear and Semi-Logrithmic plots of Regimen C and D are shown in the following figures.

Figure 1: Mean Plasma Lamotrigine Concentration Regimen C vs. Regimen D

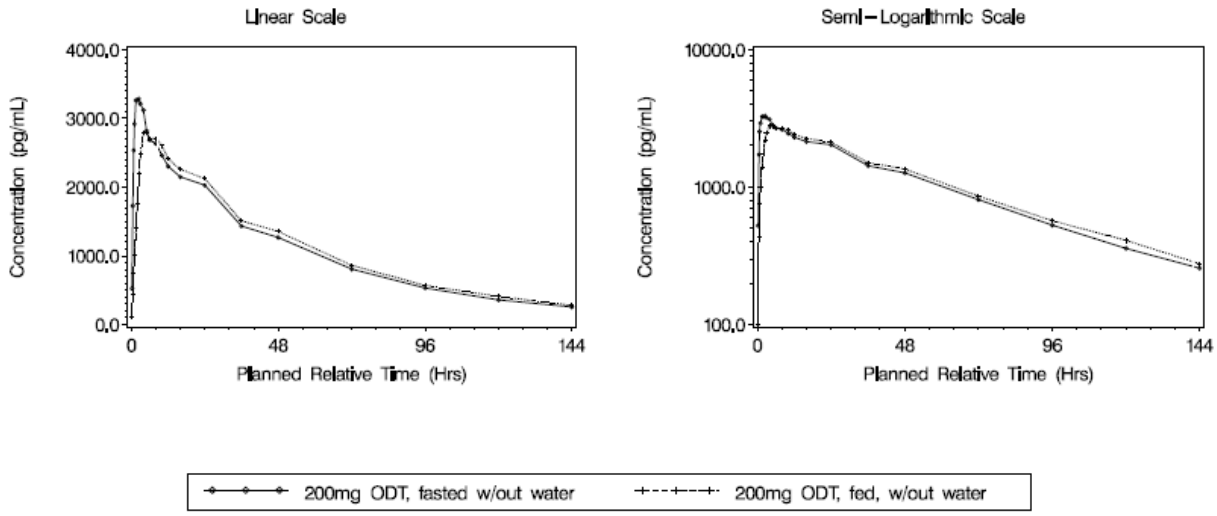


Effect of Food on Lamotrigine 200 mg Oral Disintegrating Tablet

The 90% CI of the ratio lamotrigine 200 mg ODT, fed: fasted for AUC(0–∞) were inside the equivalence range 0.800 to 1.250 indicating no effect of food on AUC(0–∞) of lamotrigine 200 mg ODT. However, for Cmax, the lower limit of the 90% CI of the ratio lamotrigine 200 mg ODT, fed: fasted was slightly lower than the limit (0.789). On average, AUC(0–∞) for lamotrigine 200 mg ODT was very similar (0.5% lower) after food compared with fasted condition.

Table 7: Effect of Food on the 200 mg ODT	
Ratio of Geometric Least Square Means (90% Confidence Interval)	
Parameter	Effect of Food on lamotrigine 200 mg ODT (Treatment E:C)
AUC (0-inf)	0.995 (0.878, 1.128)
Cmax	0.843 (0.789, 0.901)

Figure 2: Mean Plasma Lamotrigine Concentration Regimen E vs. Regimen C

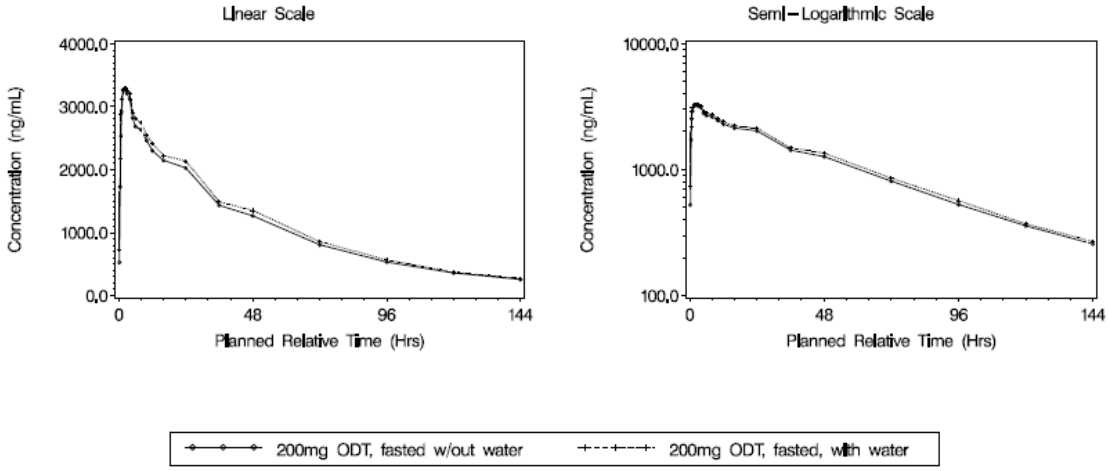


Effect of Water on Lamotrigine 200 mg Oral Disintegrating Tablet

For both AUC(0–∞) and Cmax, the 90% CI of the ratio lamotrigine 200 mg ODT, fasted, with water: lamotrigine 200 mg ODT fasted, without water were inside the equivalence range 0.800 to 1.250 indicating lack of effect of water on lamotrigine 200 mg ODT.

Table 8: Effect of Water on the 200 mg ODT	
Ratio of Geometric Least Square Means (90% Confidence Interval)	
Parameter	Effect of Water on lamotrigine 200 mg ODT (Treatment F:C)
AUC (0-inf)	1.041(0.918, 1.181)
Cmax	1.005 (0.940, 1.074)

Figure 3: Mean Plasma Lamotrigine Concentration Regimen F vs. Regimen C



Between Subject Coefficient of Variation

The pooled between-subject CV from the statistical analyses were 41.0% and 21.1% for AUC(0–∞) and Cmax respectively. For AUC(0–∞) of lamotrigine this is slightly higher than what the study was powered on (32.7%). A summary of the between-subject CV by Regimen for primary pharmacokinetic parameters is presented in Table 9.

Table 9. Summary of Between-Subject Coefficient of Variation

Parameter	Regimen C	Regimen D	Regimen E	Regimen F
AUC(0–∞)	43.44	37.37	44.88	37.94
Cmax	20.035	21.991	19.333	22.866

Source Data: Table 11.2
AUC(0–∞) = Area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time, Cmax = Maximum observed serum concentration;
Regimen C: 200mg ODT disintegrated/fasted
Regimen D: 200mg IR swallowed with water/fasted
Regimen E: 200mg ODT disintegrated/fed
Regimen F: 200mg ODT swallowed with water/fasted

DISCUSSION AND CONCLUSIONS

Bioequivalence of the 200 mg ODT formulation administered without water to the commercial 200 mg IR tablet:

The lamotrigine ODT formulation, administered without water, was shown to be bioequivalent to the approved lamotrigine IR tablet, as the 90% CI around the ratios for Cmax and AUC(0-∞) were entirely contained within the equivalence limits (0.80–1.25).

Effect of Food on the Bioavailability of the 200 mg Lamotrigine ODT:
Relative to the lamotrigine 200 mg ODT in the fasted state, food did not affect lamotrigine AUC(0-∞) when the 200 mg ODT formulation was administered immediately after a high fat breakfast, since point estimates and 90% CI for AUC(0–∞) were entirely contained within the equivalence limits (0.800–1.250). In contrast, for the same comparison with Cmax, the lower end of its 90% CI (0.789) was slightly outside the equivalence range. Administration of lamotrigine ODT in the fed state resulted in a slight decrease in maximal systemic exposure, but little overall change in total systemic lamotrigine exposure.

Effect of Dosing With and Without Water on the Bioavailability of the 200 mg Lamotrigine ODT:
The lamotrigine ODT formulation, swallowed with water, was established to be bioequivalent to the lamotrigine ODT tablet disintegrated in the mouth, without water, as point estimates and 90% CI for Cmax and AUC(0–∞) were entirely contained within the equivalence limits (0.800–1.250). Thus lamotrigine ODT can be taken with or without water.

Safety Evaluation:
The sponsor's safety and tolerability evaluation needs to be evaluated by the medical officer. The sponsor stated that lamotrigine 200 mg was well tolerated in all regimens in this study and that, overall, the safety and tolerability profile of the ODT formulation was at least as good as the IR formulation.

Organoleptic Results:
The results of the organoleptic questionnaire indicated that the majority of subjects in Regimens C and E felt the tablet dissolved instantly, were satisfied with the time it took to dissolve, felt the tablet was smooth in the mouth, were satisfied with the flavor and found the strength of the flavor pleasant, found the aftertaste pleasant and were satisfied with it and found the tablet convenient and easy to use. The majority of subjects in Regimen D would prefer to use a tablet requiring water to one that dissolved but these subjects had not used the ODT tablet. These results indicate that subjects who had received ODT were generally satisfied with the experience.

Conclusions

- Bioequivalence of the lamotrigine 200 mg ODT formulation was established relative to the currently approved lamotrigine 200 mg IR tablet (LAMICTAL™ compressed tablets 200 mg).
- There was no effect of food on lamotrigine (200 mg ODT) formulation for AUC(0–∞). For Cmax, the lower limit of the 90% confidence interval (CI) of the ratio of lamotrigine 200 mg ODT, fed: lamotrigine 200 mg ODT, fasted was slightly lower than the lower limit of the acceptance range (80-125%).
- Lack of effect of swallowing whole with water on lamotrigine 200 mg ODT formulation was established both for AUC(0–∞) and Cmax.

- Lamotrigine 200 mg was generally well tolerated in all regimens in this study. The incidence of AEs was similar in all treatment groups and the most frequent AE was headache. The incidence of drug-related AEs was slightly lower in Regimen C compared with Regimens D-F and the most frequent drug-related AE was headache. There were no SAEs.
- The organoleptic questionnaire indicated that subjects who had received ODT were generally satisfied with the time to disintegration, flavor, strength of flavor, mouth feel and aftertaste.

4.2. Study LBI108614 (Pilot Study)

Study LBI108614

(Lamotrigine, orally disintegrating tablet selection of taste-masking techniques in healthy subjects, GI267119)

TITLE:

An open-label, randomized, single-dose, parallel-group study to evaluate the pharmacokinetic characteristics, safety and tolerability of up to two formulations (with different taste-masking approaches) of an orally disintegrating tablet (ODT) of lamotrigine at 25mg and 200mg versus the immediate-release (IR) lamotrigine in healthy subjects

Phase: I

Compound Number: GI267119

Study Dates: Initiation Date: 28 Dec 2006
Completion Date: 25 Jan 2007
Date of Report: October 2007

Primary Investigator: Dr. C. J. Kissling MD
MDS Pharma,
621 Rose Street, PO Box 80837,
Lincoln, NE68502, USA

OBJECTIVES

Primary Objectives:

- To determine the pharmacokinetic characteristics of LAMICTAL™ (lamotrigine) following administration of 25mg and 200mg doses of two lamotrigine orally disintegrating tablet (ODT) formulations (two taste-masking approaches) with reference to the marketed 25mg and 200mg tablets of LAMICTAL immediate release (IR) formulation, with the aim of selecting the lamotrigine ODT taste-masking approach for further clinical development.

Secondary Objective:

- To investigate the safety and tolerability of lamotrigine following single oral doses formulated as an ODT
- To collect organoleptic data on ODT formulations.

Primary Endpoint:

- Lamotrigine area under the serum concentration curve to infinity (AUC(0-∞)) and peak serum concentration (Cmax), for each of the ODT and the corresponding IR tablet.

Secondary Endpoint:

- Time to peak serum concentration (tmax) and serum half life (t½), for each ODT and the corresponding IR tablet
- Adverse events (AEs), changes in biochemistry, hematology, urinalysis parameters, electrocardiogram (ECG) parameters, blood pressure and heart rate
- Organoleptic data: time to disintegration, taste, flavor, convenience, mouth feel and acceptability

STUDY DESIGN AND TREATMENT ADMINISTRATION:

Randomized, single-dose, open-label, parallel-group study of orally disintegrating (ODT) lamotrigine tablet formulations designed with the option to evaluate up to two different taste-masking formulations in two separate parts: Part A (microencapsulation, single flavor) and Part B (granulation, two different flavors).

Eligible subjects were randomized to receive a single dose of lamotrigine ODT or marketed IR, 25mg or 200mg) in the fasting state. Subjects in Part A received one of 4 treatment options (A – D) according to a randomly assigned treatment schedule. The results from an interim analysis of PK data from Part A (based on planned concentration sampling times) resulted in the decision not to conduct Part B. The lamotrigine ODT formulation was supplied by Clinical Trial Supplies, GSK, Research Triangle Park, North Carolina, USA.

Treatment Plan:

The following table summarizes the treatments from Part A (microencapsulation) of the study:

Table 1: Treatment Plan

Treatment	Tablet strength	Formulation	Batch number
A	25mg	lamotrigine ODT formulation 1	PF397EA0001
B	200mg	lamotrigine ODT formulation 1	PF398EA0001
C	25mg	lamotrigine IR	6ZP8743
D	200mg	lamotrigine IR	4ZP9823

Subjects swallowed the IR dose with 240mL of water. Subjects receiving ODT were not given water, but were asked to let the tablet disintegrate in their mouth. For all subjects 240 mL of water was given at 2 hours post dose.

Comparisons of Interest

The relative bioavailability of lamotrigine ODT at 25mg and 200mg compared to lamotrigine IR tablet at respective dose level was assessed using point estimates and 90% confidence intervals (CIs) of geometric least square means for AUC and Cmax of lamotrigine.

The primary comparisons of interest were:

- 25mg formulation 1 lamotrigine ODT v 25mg lamotrigine IR (A v C)
- 200mg formulation 1 lamotrigine ODT v 200mg lamotrigine IR (B v D) where formulation 1 ODT was Part A (microencapsulation) and IR was marketed, compressed tablet.

Pharmacokinetic Sample Collection:

Following administration of the lamotrigine ODT or IR tablets, blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours following dosing (23 samples). Subjects remained in the clinic until after the 48-hour (Day 3) samples had been taken. During Days 4 to 7 subjects returned on a daily basis for collection of protocol specified samples up to and including the 144-hour sample.

SUBJECTS:

Sixty-four healthy male (37) or female (27) subjects (16 subjects/treatment) aged between 19 and 55 years, inclusive with a body weight >50kg (males) or >45kg (females) and body mass index within the range 19 to 30kg/m2 inclusive.

ANALYTICAL:

Blood samples were collected, allowed to clot at room temperature and then centrifuged within 35 minutes of collection at 1500g for 15 minutes at 4°C. The serum was frozen and stored at -20ºC prior to transfer for analysis. Serum samples were analyzed for lamotrigine by protein precipitation and liquid chromatography/mass spectrometry-mass spectrometry in the positive ion turbo-ionspray mode. Quality controls (QC) were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. Quality control results from this study met these acceptance criteria. A summary of the parameters is given in the following table:

Table 2: Bioanalytical Method Performance

Bioanalytical Method Performance		
Matrix		Serum
Method		LC-MS-MS
Sample Size		50 µL aliquot
Calibration Standards	Range	4-4000 ng/mL
	Date of Analysis	

	Slope (n=46)	0.002118
	Intercept	-0.000138
	Correlation Coefficient	0.999548
n=322	Interday Precison (%CV)	1.0-4.0%
n=322	Interday Accuracy	99.7-100.4%
LOQ		
n=46	LLOQ	4 ng/mL
	Precision	4.0%
	Accuracy	100.1%
n=46	ULOQ	4000 ng/mL
	Precision	1.0%
	Accuracy	100.0%
Quality Control Samples		
Low-15 ng/mL	Precision	3.2%
n=46	Accuracy (%bias)	-3.6%
Medium-350 ng/mL	Precision	1.5%
n=150	Accuracy (%bias)	-0.7%
High-3500 ng/mL	Precision	1.7%
n=150	Accuracy (%bias)	0.1%

Three samples were repeated for being 100% higher or 50% lower than the adjacent time points.

PHARMACOGENETIC ASSESSMENTS

Blood samples (~10mL) were collected from consenting subjects for pharmacogenetic (PGx) research. Fifteen subjects gave blood samples which have been retained.

PHARMACOKINETIC ASSESSMENT

Pharmacokinetic Parameters

The relative bioavailability of the lamotrigine ODT formulations at 25mg and 200mg compared to the corresponding lamotrigine currently marketed IR doses was assessed separately with point estimates of the AUC and Cmax geometric mean ratios and 90% confidence intervals (CI) using an analysis of variance. The maximum observed serum concentration, the time to reach first occurrence of Cmax, and the absorption lag time (tlag) were the actual observed values. Geometric mean (CVb%) for primary pharmacokinetic parameters, median (range) for tmax, are shown below for each regimen:

Table 3: Pharmacokinetic Parameters

Parameter	Treatment			
	25mg lamotrigine ODT	200mg lamotrigine ODT	25mg lamotrigine IR	200mg lamotrigine IR
AUC(0-24) (µg.h/mL)	5.92 (14.2)	48.4 (16.2)	5.76 (22.1)	50.8 (20.4)
AUC(0-∞) (µg.h/mL)	15.8 (18.7)	130 (31.0)	16.1 (33.7)	134 (35.1)
AUC(0-t) (µg.h/mL)	14.8 (16.0)	121 (26.3)	14.9 (30.1)	125 (30.3)
Cmax (µg/mL)	0.363 (16.6)	2.85 (17.7)	0.368 (28.6)	3.18 (20.3)
tmax (h)	2.00 (0.5, 4.00)	2.25 (0.75, 8.00)	1.50 (0.25, 3.00)	1.04 (0.50, 4.00)
t½ (h)	34.5 (19.6)	34.9 (25.0)	36.2 (28.1)	35.6 (24.7)
tlag (h)	0 (0, 0.05)	0 (0, 0.03)	0 (0, 0)	0 (0, 0)

The ratio of the geometric least squares means and corresponding 90% CI indicated similar lamotrigine exposure from both the ODT and IR formulations at both tablet strengths. Although this study was not formally powered for bioequivalence, all of the 90% CI for primary comparisons of interest of lamotrigine ODT compared to lamotrigine IR for AUC(0-∞) and Cmax fell within the standard 0.80 to 1.25 criteria with the exception of the lower limit (0.791) for Cmax for the 200mg comparison, which was just outside the range.

Table 4: Statistical Results for AUC and Cmax

Lamotrigine PK Parameter	Ratio of Geometric Least Squares Means (90% CI)	
	25mg ODT vs 25mg IR	200mg ODT vs 200mg IR
AUC(0-∞)	0.980 (0.823, 1.167)	0.968 (0.813, 1.152)
Cmax	0.988 (0.872, 1.118)	0.896 (0.791, 1.014)

The coefficient of variation between regimens was determined for the primary PK parameters. The results are shown below.

Table 5: Comparison of Between Regimens for Coefficient of Variation of the Primary Pharmacokinetic Parameters

	25mg lamotrigine ODT	25mg lamotrigine IR	200mg lamotrigine ODT	200mg lamotrigine IR
AUC(0-∞)	18.7%	33.7%	31.0%	35.1%
Cmax	16.6%	28.6%	17.7%	20.3%

Data Source: Table 11.2

SAFETY ASSESSMENTS

The sponsor stated that the lamotrigine ODT and marketed IR tablets were well tolerated. There were no SAEs and no withdrawals due to AEs. There were no laboratory values, vital signs or ECG values of clinical concern following dosing with these formulations.

ORGANOLEPTIC QUESTIONNAIRE DATA

The majority of ODT subjects said their tablets disintegrated immediately in the mouth.
The disintegration time of ODT measured by clinic staff showed that on average the smaller 25mg tablet disintegrated faster than the 200mg tablet as would be expected based on size. Generally the two formulations were comparable in acceptability, with the majority of subjects indicating both ODT and IR formulations were neutral to pleasant in taste and easy to take.

DISCUSSION AND CONCLUSIONS

The study protocol allowed for the evaluation of two lamotrigine ODT formulations. Formulation 1 (microencapsulation) was tested first and showed similar PK to the IR tablet. The ODT was well tolerated with satisfactory outcome from the organoleptic questionnaire. Consequently a second ODT formulation was not studied and the study was terminated after Part A. The study concluded:

- Following oral administration of 25mg and 200mg lamotrigine ODT, there was no apparent delay in absorption of lamotrigine compared to lamotrigine IR, because median tlag times were zero and lamotrigine serum concentrations were generally detectable in the first post dose sample at 15 minutes.
- Administration of lamotrigine ODT, without water, resulted in an apparent slight delay in peak concentrations of lamotrigine compared to the IR formulation. Based on median lamotrigine tmax values, the delay was in the order of 0.5 to 1.25 hours. However, one subject (Subject 131) who received 200mg ODT displayed a tmax of 8 hours, although it is noteworthy that this subject's concentrations were generally similar over the 4-to-12 hour post dose period. Examination of the distribution of lamotrigine tmax, shows that following ODT, a more even distribution is evident over the 4-hour post dose period while with lamotrigine IR, the majority of subjects displayed tmax within 2 hours following dosing.
- Generally, estimates of lamotrigine elimination half-life were consistent following both lamotrigine 25mg and 200mg ODT and IR (approximately 35 hours).
- The between subject CV observed for AUC(0-∞) and Cmax of lamotrigine was generally greater in the IR dosed subjects compared with the ODT results, especially at the lower dose.
- Lamotrigine systemic exposure, in terms of Cmax and AUC, was generally comparable for lamotrigine ODT and IR at corresponding dose strengths. Mean values for %AUCex were $\leq$10% and similar across all regimens.
- Both dose strengths and formulations were well tolerated. There was no new safety issue following dosing with ODT formulation.

4.3. Analytical Method

HPLC-MS/MS Method for determination of Lamotrigine in Human Serum
Reference Number: *GI267 1 19HUSEVALC*

Method: GI267119 (lamotrigine) in human serum over the range of 10 - 10000 ng/rnL was determined by LC-MS/MS. Lamotrigine is extracted from 25 µL of human serum by protein precipitation using acetonitrile containing an isotopically labeled internal standard ($^{15}N_5$ $^{13}C_2$]-G1267119). Extracts were analyzed by HPLC-MS/MS using a TurboIonSpray™ interface and multiple reaction monitoring. The conditions of the Liquid Chromatography system and the Mass Spectrometry system are shown in the following tables.

Table 1: Summary of HPLC-MS/MS system Conditions

HPLC Conditions:

Autosampler	CTC HTS PAL
Needle Wash 1	Water containing 10% acetonitrile
Needle Wash 2	Methanol containing 50% acetonitrile
Typical Injection Volume	10 µL
Chromatography System	Shimadzu 10ADvp
Flow Rate	0.45 mL/min
Analytical Column	50 x 2.1mm i.d. Inertsil ODS-3 3 µm, Varian
Column Temperature	Room temperature
Run Time/Data Acquisition Time	1.5 minutes/1.5 minutes
Mobile Phase	2mM ammonium formate (pH 8.5) containing 50% methanol

Alternative, equivalent HPLC equipment may be used as appropriate. Minor changes to chromatographic conditions may be made and the details recorded

MS/MS Conditions:

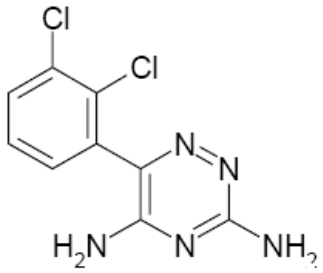
Mass Spectrometer	(b) (4)
Split Ratio	NA
Ionisation Interface and Temperature	TurboIonSpray® at 400°
Pause Time	5 msec
Nebuliser Gas (Nitrogen)	12
Turbo Gas Flow (Nitrogen)	8 L/min
Curtain Gas Setting (Nitrogen)	8
Collision Gas Setting (Nitrogen)	6
DP Value	22
CE Value	36

Analytical method parameters are typical but may vary from instrument to instrument in order to achieve an equivalent response

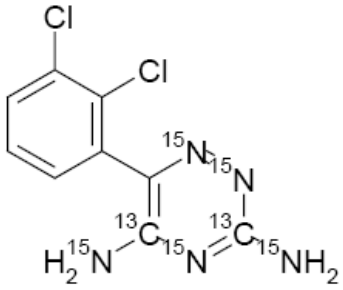
Analyte	Precursor ion (m/z)	Product Ion (m/z)	Dwell Time (msec)	Polarity	Typical R.T. (min)
GI267119	256	211	250	Positive	0.85
[$^{13}C_2$ $^{15}N_5$]-GI267119 (I.S.)	263	215	250	Positive	0.85

Masses for Precursor/Product ions are nominal

The chemical structures of the lamotrigine (GI267119) and the Internal Standard ($^{13}C_2$, $^{15}N_5$-GI267119) are shown in the following figures.



GI267119



GI267119H
(internal standard)

Figure 4.3.4: Structures of GI267119 and IS

A summary of the method validation results are shown in the following table.

Table 2: Summary of Method Validation

Calibration Model	Linear weighted $1/x^2$
Validated Range	10 to 10000 ng/mL
Precision (%CV) Within-run	≤10.5%
Precision (%CV) Between-run	≤8.7%
Accuracy (%bias)	-14.5% ≤ Bias ≤13.8%
Stability in 50% Acetonitrile : 50% Water	At least 1 month at 4°C
Stability in Human Serum	At least 24 hours at room temperature
Freeze-Thaw Stability	At least 3 cycles at -30°C
Processed Sample Stability	At least 72 hours at room temperature
Matrix Dilution	10-Fold in human serum

Calibration standards were used to establish the linearity of the method over the concentration range of 10 to 10000 ng/mL GI267119 in human serum. Validation samples to establish the bias and precision of the method were prepared from the same set of analytical standard solutions to give nominal concentrations of GI267119 in human serum at 10, 30, 800, 8000 and 10000 ng/mL. In addition to blanks and a duplicate set of calibration standards, 6 replicates at each validation sample concentration were analyzed on 4 separate occasions by the HPLC-MS/MS method.

Data Acquisition and Processing

HPLC-MS/MS data were acquired and processed (integrated) using the software application (b) (4) Calibration plots of analyte/internal standard peak area ratio versus GI267119 concentration were constructed and a weighted 1/x2 linear regression applied to the data. Concentrations of GI267119 in validation samples were determined from the appropriate calibration line, and used to calculate the bias and precision of the method.

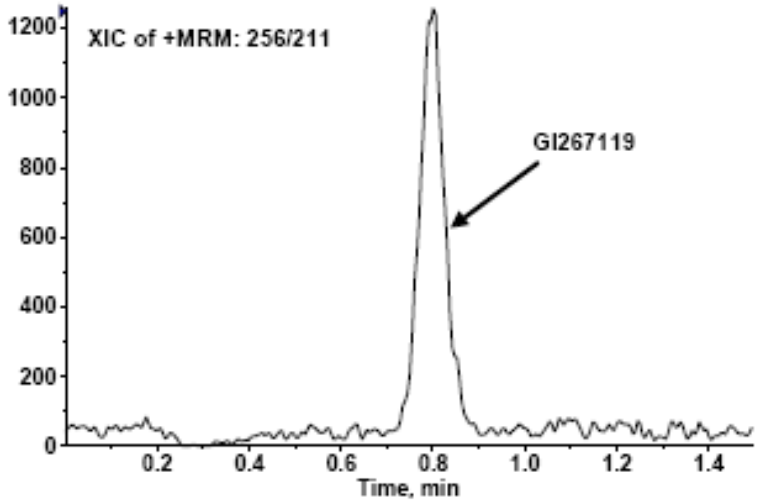
RESULTS AND DISCUSSION

Selectivity, Sensitivity and Linearity

The characteristic precursor [M+H]+ to product ion transitions, m/z 256 to 211 and 263 to 215 are consistent with the structures of GI267119 and the internal standard, respectively, and are used as multiple reaction monitoring transitions to ensure high selectivity. The selectivity of the method was established by the analysis of samples of control human serum from 6 individual volunteers by the inclusion of blank and double blank samples prepared from control human serum in validation assays. HPLC-MS/MS chromatograms of the blanks and validation samples were visually examined and compared for chromatographic integrity and potential interferences. A representative chromatogram is shown in Figure.2.

Figure 2: HPLC-MS/MS Chromatogram of Human Serum at the LLQ (10 ng/mL)

Figure 4 Representative HPLC-MS/MS Chromatogram of a Human Serum Validation Sample at the LLQ (4 ng/mL)



Linear responses in the analyte/internal standard peak area ratios were observed over the range 10 to 10000 ng/mL. The correlation coefficients obtained using $1/x^2$ weighted linear regression were better than 0.9946. The calibration data (back-calculated calibration standard data and associated parameters) are presented in Table 3.

Table 3 : Back-Calculated Standard Data and Associated Parameters for GI267119 in Human Serum

GI267119 (Serum) Calibration Standard Nominal Concentration (ng/mL)

Analytical Run	10.0	20.0	100.0	200.0	1000.0	2000.0	10000.0	Slope	Intercept	Corr. Coeff.
RUN 1	8.9	17.7	97.1	210.4	911.6	2050.7	9522.3	0.001758	0.002970	0.994694
	11.9	18.8	97.9	225.2	1056.4	1937.3	10505.7			
RUN 2	10.1	18.1	102.1	213.6	1034.9	2085.1	9513.1	0.001619	0.003219	0.995651
	11.2	16.3	97.8	217.6	1007.5	2063.1	9252.5			
RUN 3	8.6	20.4	100.0	215.6	967.1	1848.9	9321.8	0.001704	-0.000915	0.996651
	11.1	20.2	98.5	222.9	1021.6	1956.7	9892.6			
RUN 4	9.4	18.4	100.7	208.4	1003.0	1962.3	9196.5	0.001319	0.001980	0.997264
	11.2	18.8	102.2	221.6	1022.6	2036.8	9572.4			

Bias and Precision

Concentrations of GI267119 in validation samples were determined from the calibration line on each occasion. At all validation sample concentrations examined, the bias is less than 15%, and is therefore acceptable. The maximum bias observed was -14.5% (Table 4). At all validation sample concentrations examined, the within- and between-run precision values are less than or equal to 15%, and are therefore acceptable. The maximum within and between-run precision values observed were 10.5% and 8.7%, respectively.

Table 4: Overall Statistics: Bias, Precision for GI267119 in Human Serum

Table 2 Overall Statistics: Bias, Precision for GI267119 in Human Serum					
	GI267119 (Serum) ng/mL				
	10.0	30.0	800.0	8000.0	10000.0
Mean (ng/mL)	10.5	31.5	815.1	7644.3	10005.2
S.D.	1.0	2.8	45.9	630.8	522.7
Precision (%)	9.0	8.8	5.6	8.3	5.2
Bias (%)	5.5	4.9	1.9	-4.4	0.1
N	24	24	24	24	24
Avg. within run Precision	7.2	8.4	2.7	3.0	2.5
Between Run Precision	6.3	3.0	5.6	8.7	5.2

Stability in Analytical Solutions
The stability of analytical stock solutions of GI267119 in 50% acetonitrile : 50% water at 1 mg/mL, 4 µg/mL and 0.2 µg/mL stored at 4°C was assessed by comparing the mean peak area ratios of stock solutions after storage for 1 month against that of freshly prepared solutions using LC-MS/MS (in replicates of 6). The differences are less than 5%, and indicates that GI267119 is stable in analytical solutions of 50% acetonitrile: 50% water stored at 4°C for at least 1 month.

Stability in Biological Matrix
The stability of GI267119 in spiked human serum samples stored at room temperature was assessed at 30 and 8000 ng/mL (in replicates of 6) by comparing the mean concentrations of samples extracted after storage for 24 hours against those of the samples extracted immediately upon spiking. The difference is less than 15%, and indicates that GI267119 is stable in human serum stored at room temperature for at least 24 hours.

Stability During Freeze-Thaw Cycles
The stability of GI267119 in spiked human serum samples after 3 freeze-thaw cycles from -30°C to room temperature was assessed at 30 and 8000 ng/mL (in replicates of 6) by comparing the mean concentrations against those of the freshly prepared spiked samples. The freeze-thaw stability difference is less than 15% and indicates that GI267119 is stable in human serum after at least 3 freeze-thaw cycles from -30°C to room temperature.

Stability in Processed Samples
The stability of GI267119 in processed samples of human serum was assessed by re-injecting validation run batch number 1 after storage at room temperature for 72 hours against freshly prepared calibration standards from validation run batch number 3. The accuracy, precision and sensitivity of these samples were found to be acceptable on re-injection, indicating that the processed samples were stable when stored at room temperature for at least 72 hours.

58 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio Review Section-_____

VI. FILING FORM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-251	**Brand Name**	Lamictal
OCP Division (I, II, III)	I	**Generic Name**	Lamotrigine
Medical Division	Neuropharm	**Drug Class**	Epilepsy/Bipolar
OCPB Reviewer	Carol Noory	**Indication(s)**	Adjunctive therapy for partial seizures
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Orally disintegrating tablets 25 mg, 50 mg, 100 mg, 200 mg
		Dosing Regimen	
Date of Submission	November 28, 2007	**Route of Administration**	Oral
Estimated Due Date of OCP Review	May 15, 2008	**Sponsor**	GlaxoSmithKline
PDUFA Due Date	9/28/2008	**Priority Classification**	Standard
Division Due Date	8/27/2008		
1.1.1.1.			

Clin. Pharm. and Biopharm. Information

Summary: Lamictal is indicated for adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients. It is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug. LAMICTAL is also approved for use in the maintenance treatment of bipolar I disorder to delay time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy. Lamictal ODT is a new dosage form for the same indications.

The Pharmacokinetic portion of this submission consists of one pilot study (LBI108614) conducted using two prototype ODT formulations to compare two taste-masking methods and a four-arm parallel study (LBI108617) to demonstrate the BE of the ODT formulation to the approved conventional LAMICTAL tablet. This study also investigated the effect of food and water on the bioavailability of the ODT formulation. The orally disintegrating tablet information was integrated into the labeling of the LAMICTAL immediate-release tablet and chewable tablet. A deferral was granted by the OND for pediatric studies. A waiver for biostudies for the lower 25 mg, 50 mg and 100 mg ODT should be addressed by the chemist. The sponsor states that all four strengths are manufactured from a common blend with different tablet strengths.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	
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:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
renal impairment:	-			
hepatic impairment:	-			
PD:				

Phase 2:				
Phase 3:				
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:	X			Conventional IR tablet was used as the reference
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Parallel design; single dose	X	**2**	2	Pivotal Study LBI108617 and Pilot Study LBI108614
Food-drug interaction studies:	**X**			Study LBI10617 included a Food-drug interaction study and a water-drug interaction study
Dissolution:	**-**			
(IVIVC):	**-**			
Bio-waiver request based on BCS	**-**			
BCS class	**-**			
III. Other CPB Studies				
Genotype/phenotype studies:	**-**			
Chronopharmacokinetics	**-**			
Pediatric development plan	**-**			
Literature References	**X**			
Total Number of Studies		**3**	**3**	
Filability and QBR comments				

1.1.1.2.	"X" if yes	*Comments*
1.1.1.3. Application filable ?	**X**	This submission contains results from 2 in-vivo studies: 1) A pilot parallel study compared two different taste masking methods for the 25mg and 200 mg ODT compared to the 25 mg and 200 mg IR tablet. 2) A Pivotal, four-arm parallel BE study comparing the 200 mg ODT to the 200 mg IR under FASTED conditions, the ODT given under FED conditions and when dosed without water under fasted conditions. Results: • BE to the highest strength marketed IR tablets • Food effect was determined from the Pivotal Study: the 90% CI for AUC0-inf was within the 80-125% interval, while the CI for Cmax fell below the lower limit (avg: 84.7 range: 78.9-90.4) • The evaluation of the effect of co-administration with water on the pharmacokinetics of the proposed dosage form was also determined from the Pivotal Parallel BE study (CI between 80-125% for both AUC0-inf and Cmax). A biowaiver was requested for pediatric studies, however; the OND granted a deferral rather than a waiver.
1.1.1.4. Comments sent to firm ?		
QBR questions (key issues to be considered)	I. Is the 200 mg orally disintegrating LAMICTAL formulation bioequivalent to the marketed 200 mg immediate release LAMICTAL Tablets? II. Are the pharmacokinetics of the ODT formulation of LAMICTAL 200 mg altered in the presence of food and water?	
Other comments or information not included above	Please request a DSI inspection of the pivotal study (Study LBI-108617) **Clinical:** Convance Clinical Research Unit 1341 West Mockingbird Lane Suite 400 Dallas, Texas 75247 **Analytical:** WorldWide Bioanalysis Drug Metabolism and Pharmacokinetics GlaxoSmithKline R&D; 3030 Cornwallis Road, RTP, NC 27709 USA	
Primary reviewer Signature and Date	Carol A. Noory	
Secondary reviewer Signature and Date	Ramana Uppoor	

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

/s/

Carol Noory
8/28/2008 03:26:10 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/28/2008 03:41:24 PM
BIOPHARMACEUTICS