The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: LAM100034

Title: A Multicenter, Double-Blind, Randomized, Parallel-group Evaluation of LAMICTAL Extended-release Adjunctive Therapy in Subjects with Partial Seizures

Rationale: Lamotrigine extended-release (LTG-XR) is a new, enteric-coated, extended release LTG formulation that may allow subjects with seizures to be on a once daily dosing regimen. This formulation should allow for a reduction in daily trough-to-peak fluctuations in LTG-XR serum concentrations compared to LTG immediate release formulation. The current study investigated the efficacy, safety, and pharmacokinetics (PK) of adjunctive therapy with LTG-XR in subjects 13 years of age and older with partial seizures.

A 52-week open-label continuation phase was included in this study in order to evaluate the long-term tolerability of adjunctive treatment with LTG XR in adults with partial seizures.

Phase: III

Study Period: 15 Oct 2004 to 17 July 2007

Study Design: An international, multicenter, double-blind, randomized, parallel-group treatment phase, followed by a 52-week open-label continuation phase.

Centres: Nine countries participated in this study

Indication: Adjunctive therapy for partial seizures

Treatment: After completion of the 8-week Baseline Phase, subjects were randomized to receive adjunctive therapy with either LTG-XR or placebo (PBO) and then began the 7-week Escalation Phase followed by the 12-week Maintenance Phase. Subjects were assigned to one of three dosing schedules depending on their concurrent antiepileptic drug(s) (AED):

1. A dosing schedule for subjects taking concurrent valproate (VPA) with or without another AED. The target maintenance dose was 200mg/day.
2. A dosing schedule for subjects taking concurrent enzyme-inducing AEDs (EIAEDs), with or without another AED other than VPA. The target maintenance dose was 500mg/day.
3. A dosing schedule for subjects taking concurrent AED(s) other than VPA and EIAEDs. The target maintenance dose was 300mg/day.

In the Continuation Phase, subjects received open-label LTG-XR for 52 weeks.

Objectives: The primary objective of the double-blind phase of the study was to assess the efficacy of once-daily adjunctive therapy with LTG XR in subjects with partial seizures.

The primary objective of the continuation phase of the study was to evaluate the long-term tolerability and safety of adjunctive once-daily LTG-XR in subjects with partial seizures

Primary Outcome/Efficacy Variable: The primary endpoint was the median percent change from Baseline in partial seizure frequency during the entire Double-Blind Treatment Phase. For the Continuation Phase, safety was primarily assessed by recording of adverse events (AEs).

Secondary Outcome/Efficacy Variables: The Secondary endpoints for the Double-Blind Phase consisted of:

- Percent change from Baseline in partial seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase;
- Proportion of subjects with ≥25%, ≥50%, ≥75% or 100% reduction in partial seizure frequency during the entire Double-Blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase;
- Time to ≥50% reduction in seizure frequency;
- Type and incidence of treatment-emergent adverse events (AEs);
- Change from Baseline in body weight;
- Proportion of subjects with improved clinical status on the Investigator assessment of subject's clinical status questionnaire and subject's satisfaction with seizure control;
- Serum concentrations and population pharmacokinetic parameters for LTG-XR;
- For subjects ≥16 years of age if the questionnaire had been validated for the language of the country where the study was to be conducted, change from baseline in Profile of Mood States (POMS), Center for

Epidemiological Studies-Depression Scale (CES-D), Neurological Disorders Depression Inventory-Epilepsy (NDDI-E, 46-item research version), Quality of Life in Epilpesy (QOLIE-31-P), Liverpool Adverse Experience Profile (AEP), Seizure Severity Questionnaire (SSQ), Epworth Sleepiness Scale (ESS) scores.

For the Continuation Phase, daily seizure diaries were maintained by subjects and transcribed into the CRF at each visit.

Statistical Methods: Assuming an estimated pooled standard deviation (SD) of 3.5 seizures per week and a baseline rate of 4 seizures/week, 132 randomized subjects would have provided 90% power to detect a 50% difference between treatment groups at a two-sided 5% alpha level based on a t-test. Assuming a 35% drop-out rate during the Baseline Phase, approximately 204 subjects were planned to be enrolled in order to randomize 132 subjects. Subjects were centrally randomized in a 1:1 ratio to receive either LTG-XR or matching PBO.

The following 3 populations were considered for analyzing the data in the Double-Blind Phase: 1) the Intent-to-Treat (ITT) Efficacy Population was defined as all subjects who took ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment in the Double-Blind Treatment Phase, 2) the Per-Protocol Efficacy Population was defined as all subjects who completed the Double-blind Treatment Phase, excluding those with major protocol violations and 3) the Safety Population was defined as all subjects who took ≥1 dose of the study drug.

The primary efficacy endpoint was the median percent change in average weekly partial seizure frequency from baseline during the Double-Blind Treatment Phase. The Wilcoxon Rank Sum test was used for analysis on the ITT and Per-Protocol Populations.

Since there were primary and key secondary comparisons of interest, the overall Type I error was controlled by using a fixed sequential testing method for the following key secondary endpoints:

- Time to ≥50% reduction, based on change from Baseline in seizure frequency
- Change from Baseline in weight
- Health Outcomes Questionnaires [POMS, QOLIE 31P, ESS, SSQ].

Testing of these key secondary endpoints was conducted only if the test for the primary efficacy endpoint was statistically significant. If the primary efficacy endpoint test was not significant, no further testing was conducted, and no claims of significance could be made for the primary or any key secondary endpoints.

In the Continuation Phase, data were summarized using descriptive statistics; no hypothesis testing was undertaken. Unless otherwise noted, continuous variables were summarized using the mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized using frequency counts and percentages.

The Safety Population, used for safety/tolerability analyses for the Continuation Phase, was defined as all subjects who took at least one dose of study medication during the Continuation Phase. The Intent-to-Treat Population, used for analyses of seizure frequency, was defined as all subjects who took at least one dose of study medication during the Continuation Phase and had at least one post-baseline seizure assessment during the Continuation Phase.

Study Population: The study included male or female subjects ≥13 years of age who had a confident diagnosis of epilepsy with partial seizures for more than 24 weeks prior to the Baseline Phase and who had been receiving treatment with a stable regimen of 1 or 2 AEDs for at least 4 weeks prior to starting the Baseline Phase. Subjects must have had a documented history of partial seizures, and the investigator must have judged, based on the subject's previous seizure history, that the subject was likely to have at least 8 partial seizures during the 8-week Baseline Phase. Subjects could not be pregnant, receiving felbamate, have had status epilepticus within the 24 weeks prior to or during the Baseline Phase, or have exhibited any primary generalized seizures. Subjects could not have received prior treatment with LTG. In order to be eligible for randomization into the Double-Blind Phase, subjects must have had at least 8 partial seizures (i.e., simple or complex partial seizures with or without secondary generalization) during an 8-week (i.e., 56 days) Baseline Phase with at least one partial seizure occurring during each 4-week (i.e., 28 day) period.

Subjects were eligible to participate in the open-label continuation phase if the double-blind treatment phase of the study. Subjects who did not meet the minimum seizure criteria required for randomization to the double-blind phase (i.e., baseline failures) were also allowed to enter the open-label continuation phase.

Sujbect Accountability		
Double-blind Treatment Phase	**PBO**	**LTG-XR**
Number of Subjects:		
Planned, N	66	66
Randomized, N	122	121
Completed, n (%)	106 (87)	97 (80)
Total Number Subjects Withdrawn, n (%)	16 (13)	24 (20)
Withdrawn Due to AEs, n (%)	2 (2)	11 (9)
Withdrawn Due to Lack of Efficacy n (%)	0	0
Withdrawn for Other Reasons, n (%)	14 (11)	13 (11)
Open-label Continuation Phase	**LTG-XR**	
Number of Subjects:		
Entering the continuation phase, N	235	
Completed, n (%)	185 (79)	
Total Number Subjects Withdrawn, n (%)	50 (21)	
Withdrawn Due to AEs, n (%)	14 (6)	
Withdrawn Due to Lack of Efficacy n (%)	7 (3)	
Withdrawn for Other Reasons, n (%)	36 (15)	
Demographics (ITT Population)		
Double-blind Treatment Phase	**PBO**	**LTG-XR**
N	120	116
Females:Males	57:63	62:54
Mean Age, years (SD)	37.6 (14.32)	35.8 (12.68)
White- White/Caucasian/European Heritage, n(%)	83 (69)	77 (67)
Open-label Continuation Phase	**LTG-XR**	
N	232	
Females:Males	118:114	
Mean Age, years (SD)	37.1 (13.2)	
White, n(%)	154 (66)	
Primary Efficacy Results (ITT Population) for Double-Blind Phase		
Percent Reduction from Baseline in Partial Seizure Frequency During the Entire Treatment Phase	**PBO N=120**	**LTG-XR N=116**
N	120	116
Median (Range)	24.5 (-231, 100)	46.6 (-236, 100)
Estimated Difference	19.20	
95% confidence interval (CI) for Difference	9.5, 28.8	
p-value	0.0001	
Secondary Outcome Variables (ITT Population)		
Double-blind Treatment Phase		
Percent Reduction in Partial Seizures		
Escalation Phase	**PBO**	**LTG-XR**
N	120	116
Median (Range)	15.6 (-222, 100)	29.8 (-266, 100)
Estimated Difference	12.40	
95% CI for Difference	1.3, 22.9	
Maintenance Phase	**PBO**	**LTG-XR**
N	116	108
Median (Range)	26.8 (-270, 100)	58.4 (-139, 100)
Estimated Difference	31.60	
95% CI for Difference	19.5, 41.0	
Last 8 Weeks of Maintenance Phase	**PBO**	**LTG-XR**
N	116	108
Median (Range)	26.9 (-264, 100)	66.7 (-146, 100)
Estimated Difference	33.3	
95% CI for Difference	20.0, 44.5	

Distribution of Percent Change in Seizure Frequency	**PBO N=120 n (%)**	**LTG-XR N=116 n (%)**
Entire Treatment Phase, n		
N	120	116
≥25% Reduction	59 (49.2)	79 (68.1)
≥50% Reduction	25 (20.8)	51 (44.0)
≥75% Reduction	6 (5.0)	21 (18.1)
100% Reduction	1 (<1)	3 (2.6)
Escalation Phase		
N	120	116
≥25% Reduction	52 (43.3)	61 (52.6)
≥50% Reduction	28 (23.3)	33 (28.4)
≥75% Reduction	7 (5.8)	14 (12.1)
100% Reduction	2 (1.7)	3 (2.6)
Maintenance Phase		
N	116	108
≥25% Reduction	62 (53.4)	86 (79.6)
≥50% Reduction	36 (31.0)	66 (61.1)
≥75% Reduction	14 (12.1)	41 (38.0)
100% Reduction	5 (4.3)	22 (20.4)
Last 8 Weeks of Maintenance Phase		
N	116	108
≥25% Reduction	64 (55.2)	85 (78.7)
≥50% Reduction	36 (31.0)	70 (64.8)
≥75% Reduction	19 (16.4)	50 (46.3)
100% Reduction	6 (5.2)	23 (21.3)
Time to ≥50% Reduction in Seizure Frequency For All Partial Seizures (in Weeks)	**PBO N=120 n (%)**	**LTG-XR N=116 n (%)**
2	9 (7.5)	14 (12.1)
4	10 (8.3)	22 (19.0)
8	16 (13.3)	34 (29.3)
12	17 (14.2)	39 (33.6)
16	22 (18.3)	45 (38.8)
19	25 (20.8)	50 (43.1)
Investigator's Global Assessment at End of Study	**PBO n (%)**	**LTG-XR n (%)**
Overall Status, N	112	109
Any Improvement	45 (40)	65 (60)
No Change	62 (55)	34 (31)
Any Deterioration	5 (4)	10 (9)
Subject Satisfaction Questionnaire at End of Study	**PBO n (%)**	**LTG-XR n (%)**
N	112	109
Any Improvement	53 (47)	79 (72)
No Change	48 (43)	18 (17)
Any Deterioration	11 (10)	12 (11)

Health Outcomes (ITT Population), all scores listed below represent change from baseline scores

Assessment Instrument	**PBO N=120**		**LTG-XR N=116**		**Difference** (LTG-XR – PBO)
	n	**LS Mean (SE)**	**n**	**LS Mean (SE)**	
POMS Mood Disturbance Total Score					
End of Study	69	7.5 (3.36)	56	0.0 (3.73)	7.54

CES-D Total Score					
End of Study	44	2.1 (1.32)	37	0.6 (1.43)	1.51
NDDI-E 6-Item Total Score					
End of Study	32	1.3 (0.63)	28	-0.4 (0.67)	1.71
QOLIE-31P Overall Score					
End of Study	52	-5.5 (1.70)	42	-2.9 (1.89)	-2.63
AEP Total Score					
End of Study	30	2.4 (1.64)	22	2.3 (1.91)	0.11
SSQ Global Bother Score					
End of Study	32	0.91 (0.33)	27	0.81 (0.36)	0.15
ESS 8-Item Total Score					
End of Study	51	0.7 (0.55)	47	0.7 (0.57)	-0.04

Body Weight (ITT Population), changes from baseline weights		
	PBO N=120	**LTG-XR N=116**
N	119	115
Least Squares Mean (Standard Error)	0.1 (0.30)	0.1 (0.31)
Difference	-0.04	
90% CI for Difference	-0.757, 0.680	

Open-label Continuation Phase	
Weekly Seizure Frequency (All Partial Seizures)	**LTG-XR**
% Change, median (range) (positive number denotes seizure reduction)	66.3 (-194.7, 100)

Safety Results: Double-blind Treatment Phase. The time period for collecting and recording adverse events (AEs) and serious adverse events (SAEs) for randomized subjects began at randomization and ended three weeks after the last dose of study drug. In addition, SAEs that were related to study participation or were related to a concurrent medication were collected and recorded from the time the subject consented to participate in the study until he was discharged. A treatment-emergent AE was defined as any event that had increased in intensity from the Baseline Phase or had an initial onset during the Treatment Phase.

Ten Most Frequent Treatment-Emergent Adverse Events in Each Group During Double-blind Treatment Phase (Safety Population)	**PBO N=121 n (%)**	**LTG-XR N=118 n (%)**
Subjects with any AEs, n(%)	83 (69)	86 (73)
Dizziness	6 (5)	23 (19)
Headache	22 (18)	19 (16)
Diarrhea	6 (5)	9 (8)
Somnolence	6 (5)	8 (7)
Nausea	3 (2)	8 (7)
Asthenia	3 (2)	6 (5)
Tremor	1 (<1)	6 (5)
Vomiting	2 (2)	5 (4)
Depression	1 (<1)	5 (4)
Vision Blurred	3 (2)	5 (4)
Diplopia	0	5 (4)
Nasopharyngitis	15 (12)	4 (3)
Fatigue	4 (3)	4 (3)
Insomnia	6 (5)	4 (3)
Upper Respiratory Tract Infection	5 (4)	3 (3)
Toothache	4 (3)	1 (<1)
Pain in Extremity	5 (4)	2 (2)
Arthralgia	4 (3)	2 (2)
Pyrexia	5 (4)	3 (3)
Hypertension	4 (3)	0
Pruritus	4 (3)	3 (3)

Safety Results: Open-label Continuation Phase. AEs and SAEs were captured for the period from enrollment into the continuation phase to end of study.		
Ten Most Frequent Treatment-Emergent Adverse Events During Open-label Continuation Phase(Safety Population)	**LTG-XR N=235 n (%)**	
Any AE	163 (69)	
Headache	52 (22)	
Dizziness	39 (17)	
Nausea	22 (9)	
Vomiting	18 (8)	
Diplopia	15 (6)	
Insomnia	14 (6)	
Nasopharyngitis	13 (6)	
Rash	13 (6)	
Tremor	11 (5)	
Back pain	9 (4)	
Sinusitis	9 (4)	
Somnolence	9 (4)	
Serious Adverse Events, n (%) [n considered by the investigator to be related to study medication]		
SAEs During Double-blind Treatment Phase	**PBO N=121**	**LTG-XR N=118**
	n (%) [related]	**n (%) [related]**
Subjects with Any Treatment-Emergent Non-Fatal SAEs (Safety Population)	**6 (5) [0]**	**5 (4) [2]**
Gastritis erosive	1 (1) [0]	0
Pancreatitis	0	1 (<1) [1]
Vomiting	1 (<1) [0]	0
Intentional overdose	0	1 (<1) [0]
Radius fracture	1 (<1) [0]	0
Tibia fracture	0	1 (<1) [0]
Dizziness	0	1 (<1) [1]
Drop attack	1 (<1) [0]	0
Headache	0	1 (<1) [1]
Nystagmus	0	1 (<1) [1]
Partial seizures	0	1 (<1) [0]
Sepsis	1 (<1) [0]	0
Urinary tract infection	1 (<1) [0]	0
Urosepsis	1 (<1) [0]	0
Myocardial infraction	0	1 (<1) [0]
Diabetes mellitus	1 (<1) [0]	0
Hypokalaemia	1 (<1) [0]	0
Hypomagnesia	1 (<1) [0]	0
Uterine leiomyoma	1 (<1) [0]	0
Urinary retention	1 (<1) [0]	0
Cough	1 (<1) [0]	0
Subjects with Pre-Treatment Fatal SAEs	**n (%) [related]**	**n (%) [related]**
Complex Partial Seizures [Event occurred prior to treatment; subject never received study medication]	0	1 (<1) [0]
Subjects with Treatment-Emergent Fatal SAEs	**n (%) [related]**	**n (%) [related]**
None	0	0
SAEs During Open-label Continuation Phase	**LTG-XR N=235**	
	n (%) [related]	

Subjects with Any Treatment-Emergent Non-Fatal SAEs (Safety Population)	**19 (8%) [2]**
Abasia	1 (<1%) [1]
Acute cholecystitis	1 (<1%) [0]
Acute pyelonephritis	1 (<1%) [0]
Ankle fracture	1 (<1%) [0]
Astrocytoma	1 (<1%) [0]
Ataxia	1 (<1%) [1]
Brain contusion	1 (<1%) [0]
Cervical spinal stenosis	1 (<1%) [0]
Cholelithiasis	1 (<1%) [0]
Complex partial seizures	1 (<1%) [0]
Contusion	1 (<1%) [0]
Diabetic ketoacidosis	1 (<1%) [0]
Dizziness	1 (<1%) [1]
Dysarthria	1 (<1%) [0]
Food poisoning	1 (<1%) [0]
Gastritis	1 (<1%) [0]
Infection	1 (<1%) [0]
Intervertebral disc protrusion	1 (<1%) [0]
Malignant hypertension	1 (<1%) [0]
Multiple fractures	1 (<1%) [0]
Partial seizures with secondary generalization	1 (<1%) [0]
Pelvic fracture	1 (<1%) [0]
Skin laceration	1 (<1%) [0]
Skull fracture	1 (<1%) [0]
Status epilepticus	1 (<1%) [0]
Traumatic brain injury	1 (<1%) [0]
Viral gastroenteritis	1 (<1%) [0]
Viral pneumonia	1 (<1%) [0]
Vomiting	1 (<1%) [1]
	n (%) [related]
Subjects with Treatment-Emergent Fatal SAEs	**3 (1%) [2]**
Acute cardiac failure	1 (<1%) [1]
Aspiration	1 (<1%) [0]
Cardiac arrest	1 (<1%) [0]
Drug toxicity	1 (<1%) [1]
Grand mal convulsion	1 (<1%) [0]
Conclusion: See publications below.	
Publications: D. K. Naritoku, C. R. Warnock, J. A. Messenheimer, R. Borgohain, S. Evers, A. B. Guekht, V. A. Karlov, B. I. Lee and L. Ríos Pohl: Lamotrigine extended-release as adjunctive therapy for partial seizures. *Neurology* 2007;69;1610-1618 Erratum: Lamotrigine extended-release as adjunctive therapy for partial seizures. *Neurology* 2009;72;201	