Protocol Registration Receipt
09/20/2012

Grantor: CDER IND/IDE Number: 69,254 Serial Number: 0000

Study Evaluating LAMICTAL Extended-Release Therapy Added To Current Seizure Treatments In Patients With Primary Generalized Tonic-Clonic Seizures (PGTC) Seizures

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00104416

Purpose

This study is being conducted to compare the efficacy and safety of LAMICTAL (lamotrigine) extended-release with placebo in the treatment of Primary Generalized Tonic-Clonic (PGTC) seizures. LAMICTAL extended-release is an investigational drug. Placebo tablets look like LAMICTAL extended-release tablets but do not contain active medication. In this study, LAMICTAL extended-release or placebo tablets will be added to current seizure treatments.

Condition	Intervention	Phase
Epilepsy Seizures, Tonic-Clonic Epilepsy, Tonic-Clonic	Drug: lamotrigine (LAMICTAL) extended-release Drug: Placebo	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A Multicenter, Double-Blind, Randomized, Parallel-group Evaluation of LAMICTAL Extended-release Adjunctive Therapy in Subjects With Primary Generalized Tonic-Clonic Seizures

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Percent Change From Baseline in Weekly Primary Generalized Tonic-clonic (PGTC) Seizure Frequency During the Entire Double-Blind Treatment Phase [Time Frame: Baseline through end of Double-Blind Treatment Phase (up to Week 19)] [Designated as safety issue: No]

  Percent change from baseline is calculated as the number of seizures by week during the Double-Blind Treatment Phase (Treatment Week 1 up to Week 19) compared to the number of seizures per week during the Baseline Phase (Baseline Week 1 up to Week 8). A positive number equals a reduction in seizure frequency. PGTC seizures are more commonly known as gran mal seizures.

Secondary Outcome Measures:

- Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction in PGTC Seizure Frequency During the Entire Double-Blind (DB)Treatment Phase (TP), the Escalation Phase, the Maintenance Phase, and the Last 8 Weeks of the Maintenance Phase [Time Frame: Entire DB Treatment Phase (Treatment Week 1 up to Week 19), Escalation Phase (Treatment Week 1 up to Week 7), Maintenance Phase (Treatment Week 8 up to Week 19), and the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19)] [Designated as safety issue: No]

  Change in seizure frequency was calculated as the average seizure frequency during each of the following: the Entire DB Treatment Phase (Treatment Week 1 up to Week 19); the Escalation Phase (Treatment Week 1 up to Week 7); the Maintenance Phase (Treatment Week 8 up to Week 19); and the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19), minus the seizure frequency at Baseline.
- Percent Change From Baseline in PGTC Seizure Frequency During the Escalation Phase, the Maintenance Phase, and During the Last 8 Weeks of the Maintenance Phase of the Double-Blind Treatment Phase [Time Frame: Escalation Phase (Treatment Week 1 up to Week 7), Maintenance Phase (Treatment Week 8 up to Week 19), and the last 8 weeks of the Maintenance Phase (Week 12 up to Week 19)] [Designated as safety issue: No]

  Percent change from baseline is calculated as the number of seizures by week during the Escalation Phase (Treatment Week 1 up to Week 7), the Maintenance Phase (Treatment Week 8 up to Week 19), and during the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19) compared to the number of seizures per week during the Baseline Phase (Baseline Week 1 up to Week 8). A positive number equals a reduction in seizure frequency.
- Number of Participants With the Indicated Time to >=50% Reduction in Seizure Frequency in the Double-Blind Treatment Phase [Time Frame: Baseline

through end of Double-Blind Treatment Phase (up to Week 19)] [Designated as safety issue: No]

50% reduction in seizure frequency is defined as the time at which a participant first achieved and maintained a >=50% reduction in seizure frequency following exposure to at least 1 week of study drug.

- Change From Baseline in Body Weight at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  Change from baseline in body weight is calculated as the Week 19 (or last on-study measurement in Double-Blind Treatment Phase) value minus the Baseline value.
- Number of Participants With Improved Clinical Status on the Investigator's Global Assessment in the Double-Blind Treatment Phase [Time Frame: Week 19 (or last on-study assessment in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The investigators rated the participants' overall clinical status based on 7 clinical factors and an overall factor: seizure frequency, duration, and intensity; adverse experiences; social, intellectual, and motor functioning. Using a 7-point scale (marked deterioration [1], moderate deterioration [2], mild deterioration [3], no change [4], mild improvement [5], moderate improvement [6], or marked improvement [7]), the investigators assessed the participants' status compared to their condition prior to initiating study medication.
- Number of Participants With Improved Satisfaction With Seizure Control on the Subject Satisfaction Questionnaire in the Double-Blind Treatment Phase [Time Frame: Week 19 (or last on-study assessment in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  Participants were asked to rate their satisfaction with their seizure control compared to their seizure control prior to initiating study drug on a 7 point scale: marked deterioration (1), moderate deterioration (2), mild deterioration (3), no change (4), mild improvement (5), moderate improvement (6), or marked improvement (7).
- Percent Change From Baseline in Weekly PGTC Seizure Frequency During the Entire Continuation Phase (CP), the Transition Phase, the Open-Label Phase, and the Last 8 Weeks of the Open-Label Phase [Time Frame: Entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase (CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52)] [Designated as safety issue: No]

  Percent change from baseline is calculated as the number of seizures by week during the entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase (CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52) minus the number of seizures per week during the Baseline Phase (Baseline Week 1 through Week 8). A positive number equals a reduction in seizure frequency.
- Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction or >=50% Increase From Baseline in Weekly PGTC Seizure Frequency for the Entire Continuation Phase, the Transition Phase, the Open-Label (OL) Phase, and the Last 8 Weeks of the OL Phase. [Time Frame: Entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase (CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52)] [Designated as safety issue: No]

  Change in seizure frequency was calculated as the average seizure frequency during each of the following: the Entire CP (CP Week 1 up to Week 52); the Transition Phase (CP Week 1 up to Week 7); the Open-Label (OL) Phase (CP Week 8 up to Week 52); and the last 8 weeks of the Open Label Phase (CP Week 45 up to Week 52) minus the seizure frequency at Baseline. W, Week.
- Mean Change From Baseline in the Profile of Mood State (POMS) Mood Disturbance Total Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

The POMS is a self-administered 65-item questionnaire that evaluates the participants' perception of their mood state in 6 areas: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely), with higher scores indicating a more negative mood state. A total score (from 0 to 24) is obtained by summing the scores of the six domains.

- Mean Change From Baseline in the Center for Epidemiological Studies-Depression Scale (CES-D) Total Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The 20-item CES-D questionnaire is self-administered and asks respondents to report the frequency to which the 20 events were experienced over the past week. A 4-point Likert scale is used and ranges from rarely or none of the time (0) to most or all of the time (3). The total score, a sum across the 20 items (ranging from 0 to 60), determines the extent to which a participant may be experiencing depression. Higher scores indicate a higher severity of depression.
- Mean Change From Baseline in the Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) 6-Item Total Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The NDDI-E is a self-reported questionnaire composed of 46 brief phrases/words to identify mood disorders across the spectrum of depression. It was developed to capture depressive moods that are co-morbid with the disease of epilepsy or its treatment as well as to measure the depressive state of the participant. All phrases are measured on a 4-point Likert scale of Never (1) to Always/often (4) and refer to the participants' mood over the past week. Scoring is comprised of a total mood score calculated by summing the scores of 6 specific items (from 6=never to 24=always or often).
- Mean Change From Baseline in the Quality of Life in Epilepsy-31-P (QOLIE-31P) Overall Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The QOLIE-31 is a 31-item questionnaire that evaluates the participants' perception of his or her quality of life in 7 domains: seizure worry, emotional well being, energy/fatigue, cognitive functioning, medication effects, social functioning, and overall quality of life. Each domain (with scores ranging from 0 to 100) is summed and divided by the total number of questions that were answered. The overall score is derived by weighting and then summing up the seven domain scores.
- Mean Change From Baseline in the Adverse Experience Profile (AEP) Total Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The AEP is a list of 19 items covering many possible side effects attributable to drug treatment. The participants respond by assessing how much each event has been a problem for them over the past 4 weeks (1=Never a Problem to 4=Always a Problem). Each individual item can be examined; an overall adverse events score is calculated as the sum of the scores across the 19 items. The AEP total score ranges from 19 to 76, with a higher score indicating a higher degree of adverse event severity.
- Mean Change From Baseline in the Seizure Severity Questionnaire (SSQ) Global Bother Score at Week 19 Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  The SSQ is a self-reported instrument developed to assess the severity of seizures and seizure symptoms. The scale consists of 10 major clinical features/symptoms of seizures that the participants rate on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]). The Global Bother Domain is the primary score used for the analysis of the SSQ and has scores ranging from 1 to 7.
- Mean Change From Baseline in the Epworth Sleepiness Scale (ESS) 8-Item Total Score at Week 19 of the Double-Blind Treatment Phase [Time Frame: Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

The ESS is an 8-item, self-administered questionnaire that measures excessive daytime sleepiness in adults. The instrument captures information on the extent to which the participant would be likely, or not, to fall asleep in certain situations. The stimulus question is: How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Questions are answered on a 4-point scale (would never doze [0] to high chance of dozing [3]). The total score ranges from 0 to 24, where a higher score indicates a higher chance of dozing.

- Serum Concentrations and Population (POP) Pharmacokinetic Parameters for Lamotrigine [Time Frame: Blood samples drawn at Treatment Weeks 11, 15, and 19 (or last on-study measurement in Double-Blind Treatment Phase)] [Designated as safety issue: No]

  Serum samples for participants on lamotrigine were analyzed with a validated analytical method based on solid phase extraction of serum followed by High-Performance Liquid Chromatography (HPLC) Mass Spectrometry (MS)/MS analysis. The lower limit of quantification (LLQ) for serum lamotrigine was 4 nanograms (ng)/milliliter (mL), using a 50 microliter (µL) aliquot of human serum with a higher limit of quantification (HLQ) of 4,000 ng/mL. PK data cannot be reported, as PK data from several different studies have been combined into one POP/PK analysis and cannot be separated by study.

Enrollment: 153
Study Start Date: December 2004
Study Completion Date: July 2008
Primary Completion Date: July 2008

Arms	Assigned Interventions
Placebo Comparator: Placebo	Drug: Placebo Placebo control Other Names: Placebo
Experimental: lamotrigine (LAMICTAL) extended-relesase	Drug: lamotrigine (LAMICTAL) extended-release Primary experimental dosage form Other Names: lamotrigine (LAMICTAL) extended-release

Eligibility

Ages Eligible for Study: 13 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Is ≥13 years of age (male or female).
- Has a confident diagnosis of epilepsy with PGTC seizures for more than 24 weeks prior to the Baseline Phase.
- Has electroencephalogram (EEG) evidence of either spike-and-wave discharges consistent with PGTC, or at least 2 EEGs with no indication of focal abnormalities. The EEG may be historical or prospective. Investigators may use a historical EEG as long as there is appropriate documentation.
- Has a documented history of PGTC seizures with or without other generalized seizure type(s) with no focal onset, and at least 1 PGTC seizure during the eight consecutive weeks (i.e., 56 consecutive days) prior to starting the 8-week Baseline Phase.
- Has at least 3 PGTC seizures occurring anytime during an 8-week (i.e., 56 days) prospective Baseline Phase.
    - NOTE: When a historical baseline is used, the same time period cannot count for documentation of inclusion criteria 4 and 5. Additionally, innumerable seizure activity will not count towards the number of seizures required for randomization.
    - NOTE: With authorization from GSK, a maximum of four weeks (i.e., 28 days) of historical seizure data may replace up to four weeks (i.e., 28 days) of the prospective Baseline Phase for subjects providing reliable documentation of the following:
        a. complete daily seizure diary that includes the number of seizures experienced each day along with the exact classification of each seizure type for consecutive days prior to the prospective Baseline Phase
        b. stability of prescribed dosages of background antiepileptic drugs (AEDs)
        c. compliance with background AEDs.
    - All subjects permitted to use historical seizure data must complete a minimum of four weeks (i.e., 28 days) of the prospective Baseline Phase. The historical Baseline Phase and the prospective Baseline Phase must equal 56 consecutive days.
- Is currently treated with a stable regimen of one or two AED(s) for at least four weeks prior to starting the Baseline Phase (historical or prospective).
    - NOTE: Benzodiazepines used chronically will be considered to be concurrent AEDs.
    - NOTE: Subjects with surgically implanted vagal nerve stimulators (VNS) will be allowed to enter the study provided that all of the following conditions are met:
        a. VNS has been in place for at least 24 weeks prior to the Baseline Phase.
        b. The settings must remain the same for at least 28 days prior to the Baseline Phase.
        c. The settings must remain the same during the Baseline, Escalation, Maintenance and Transition Phases.
        d. The battery is expected to last for the duration of the study.
        e. VNS is counted as a "concurrent AED."
- Is able and willing to maintain an accurate and complete daily written seizure diary, or has a parent/caregiver who is able and willing to maintain an accurate and complete daily written seizure diary for the entire duration of the study.
- Is able to comply with dosing of study drugs, background AEDs and all study procedures.
- Has given written informed consent, or has a parent/legally authorized representative who has given written informed consent, prior to the performance of any study assessments.

- If female, and of childbearing potential, must be using an acceptable form of birth control, to include one of the following:
    a. Complete abstinence from intercourse for two weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (a minimum of 3 weeks).
    b. Consistent and correct use of one of the following methods of birth control:
        - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject
        - Implants of levonorgestrel
        - Injectable progestogen
        - Oral contraceptive (either combined, with at least 50mcg estrogen for women on enzyme-induced AEDs, or progestogen only)
        - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year
        - Double barrier method consisting of spermicide plus a mechanical barrier (e.g., spermicide plus a male condom or a female diaphragm).
        - NOTE: Women who have had a hysterectomy, tubal ligation, or are post-menopausal are considered to be of non-childbearing potential.

Exclusion Criteria:

- Has a history of partial seizures or interictal expression of partial seizures as evidenced by EEG NOTE: EEG may be historical or prospective.
- Has had status epilepticus within the 24 weeks prior to, or during, the Baseline Phase.
- Is taking three or more background AEDs chronically.
- Has Lennox-Gastaut syndrome.
- Is currently using or has previously used lamotrigine.
- Is currently taking felbamate.
- Is abusing alcohol and/or other substance(s).
- Has taken an investigational drug within the previous 30 days or plans to take an investigational drug anytime during the study.
- Is receiving chronic treatment with any medication that could influence seizure control. NOTE: Use of benzodiazepines is allowed.
- Is currently following the ketogenic diet.
- Is planning surgery to control seizures during the study.
- Is suffering from acute or progressive neurological disease, severe psychiatric disease, or severe mental abnormality that are likely to interfere with the objectives of the study.
- Has any clinically significant cardiac, renal, hepatic condition, or a condition that affects the absorption, distribution, metabolism or excretion of drugs.
- Is pregnant, breastfeeding, or planning to become pregnant during the study or within the three weeks after the last dose of study drug.

Contacts and Locations

Locations

United States, Arkansas

GSK Investigational Site

Little Rock, Arkansas, United States, 72205

United States, California

GSK Investigational Site

Los Angeles, California, United States, 90033

GSK Investigational Site

Santa Monica, California, United States, 90404

GSK Investigational Site

Sepuldeva, California, United States, 91343

United States, Florida

GSK Investigational Site

Ocala, Florida, United States, 34471

United States, Georgia

GSK Investigational Site

Atlanta, Georgia, United States, 30342

GSK Investigational Site

Savannah, Georgia, United States, 31405

GSK Investigational Site

Suwanee, Georgia, United States, 30024

United States, Illinois

GSK Investigational Site

Flossmoor, Illinois, United States, 60422

GSK Investigational Site

Springfield, Illinois, United States, 62702

United States, Kansas

GSK Investigational Site

Wichita, Kansas, United States, 67214

United States, Kentucky

GSK Investigational Site

Crestview Hills, Kentucky, United States, 41017

GSK Investigational Site

Louisville, Kentucky, United States, 40202

United States, Massachusetts

GSK Investigational Site

Boston, Massachusetts, United States, 02118

United States, Michigan

GSK Investigational Site

Detroit, Michigan, United States, 48202

GSK Investigational Site

Traverse City, Michigan, United States, 49684

United States, Minnesota

GSK Investigational Site

Minneapolis, Minnesota, United States, 55422

United States, Missouri

GSK Investigational Site

Kansas City, Missouri, United States, 64111

United States, Nevada

GSK Investigational Site

Las Vegas, Nevada, United States, 89106

United States, New Jersey

GSK Investigational Site

Edison, New Jersey, United States, 08818

United States, Texas

GSK Investigational Site

Dallas, Texas, United States, 75230

GSK Investigational Site

Houston, Texas, United States, 77005

United States, Virginia

GSK Investigational Site

Richmond, Virginia, United States, 23220

Argentina

GSK Investigational Site

Ciudad Autonoma de Buenos Aires, Argentina, C1221ADC

GSK Investigational Site

Ciudad Autónoma de Buenos Aires, Argentina, 1425

GSK Investigational Site

Capital Federal, Buenos Aires, Argentina, 1181

Brazil

GSK Investigational Site

Curitiba, Paraná, Brazil, 80069-900

Germany

GSK Investigational Site

Alzenau, Bayern, Germany, 63755

GSK Investigational Site

Bamberg, Bayern, Germany, 96047

GSK Investigational Site

Hattingen, Nordrhein-Westfalen, Germany, 45525

GSK Investigational Site

Koeln, Nordrhein-Westfalen, Germany, 50767

GSK Investigational Site

Limburgerhof, Rheinland-Pfalz, Germany, 67117

GSK Investigational Site

Koethen, Sachsen-Anhalt, Germany, 06366

GSK Investigational Site

Kiel, Schleswig-Holstein, Germany, 24105

India

GSK Investigational Site

Hyderabad, Andhra Pradesh, India, 500482

GSK Investigational Site

Lucknow, India, 226003

GSK Investigational Site

New Delhi, India

Korea, Republic of

GSK Investigational Site

Seoul, Korea, Republic of, 135-710

Malaysia

GSK Investigational Site

Kubang Kerian, Malaysia, 16150

Russian Federation

GSK Investigational Site
Ekaterinburg, Russian Federation, 620102

GSK Investigational Site
Moscow, Russian Federation, 111539

GSK Investigational Site
Moscow, Russian Federation, 117049

GSK Investigational Site
Moscow, Russian Federation, 107076

GSK Investigational Site
Moscow, Russian Federation, 125412

GSK Investigational Site
Moscow, Russian Federation, 105066

GSK Investigational Site
Moscow, Russian Federation, 117049

GSK Investigational Site
Samara, Russian Federation, 443095

GSK Investigational Site
St'Petersburg, Russian Federation, 197136

GSK Investigational Site
St.-Petersburg, Russian Federation, 193019

GSK Investigational Site
St.-Petersburg, Russian Federation, 194291

Ukraine

GSK Investigational Site
Kharkiv, Ukraine, 61068

GSK Investigational Site
Kyiv, Ukraine, 02660

GSK Investigational Site
Lviv, Ukraine, 79021

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Study Results

Participant Flow

Recruitment Details

All participants (par.) that complete the Treatment Phase (TP) and all Baseline Failures (par. who did not meet randomization seizure criteria necessary to qualify for the TP) are eligible to enter the Continuation Phase (CP). The CP is for long-term safety exposure to lamotrigine (LTG) extended release (XR); it is not a cross-over phase.

Pre-Assignment Details

The number of par. starting the CP does not equal the number completing the TP, as 1) the CP was optional, 2) not everyone from the TP was eligible to enter the CP, and 3) Baseline Failures were allowed to enter the CP, however they were not included in the “started" count for the TP.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	Lamotrigine (LTG) extended release (XR) once daily
Continuation Phase: Placebo/LTG	Participants who received placebo in the Double-Blind Phase and then entered the CP, in which they received LTG
Continuation Phase: LTG/LTG	Participants who received LTG XR in the Double-Blind Phase and then entered the CP, in which they received LTG
Baseline Failures	Baseline failures who entered the CP without receiving treatment in the

	Description
	Double-Blind Phase. Baseline Failures were participants that successfully progressed through the Screening Phase and completed the Baseline Phase of the Double-blind Study, but ultimately did not meet the seizure frequency criteria for randomization into the Double-Blind Treatment Phase of the study. As a result, they were not counted as having started in the Double-Blind Study, but were eligible to enter the CP of the study.

Double-Blind Phase

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Started	77	76	0	0	0
Completed	69	66	0	0	0
Not Completed	8	10	0	0	0
Adverse Event	2	1	0	0	0
Lost to Follow-up	0	1	0	0	0
Protocol Violation	0	1	0	0	0
Withdrawal by Subject	2	3	0	0	0
Pregnancy	1	0	0	0	0
Participant Did Not Take Drug	3	4	0	0	0

Continuation Phase

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Started	0	0	69	67 [1]	32
Completed	0	0	63	65	27
Not Completed	0	0	6	2	5
Adverse Event	0	0	2	0	2
Lost to Follow-up	0	0	1	0	1
Withdrawal by Subject	0	0	2	1	1
Pregnancy	0	0	1	1	0
Non-compliance	0	0	0	0	1

[1] One participant did not complete the Double-Blind Phase but was enrolled in the Continuation Phase.

Baseline Characteristics

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Baseline Measures

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Total
Number of Participants	73	70	143
Age, Continuous [1] [units: years] Mean (Standard Deviation)	28.4 (11.48)	29.4 (12.78)	28.9 (12.10)
Gender, Male/Female [2] [units: participants]			
Female	38	32	70
Male	35	38	73
Race/Ethnicity, Customized [3] [units: participants]			
African American/African Heritage	1	2	3
Asian	31	31	62
White	38	37	75
American Indian or Alaskan Native and White	2	0	2
Asian and White	1	0	1

[1] Baseline measures are on the Intent-to-Treat (ITT) Population, participants who took at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. Four and six participants did not meet the ITT definition in the Double-Blind Treatment Phase Placebo Arm and the Double-Blind Treatment Phase LTG XR Arm, respectively.

[2] Baseline measures are on the Intent-to-Treat (ITT) Population, participants who took at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. Four and six participants did not meet the ITT definition in the Double-Blind Treatment Phase Placebo Arm and the Double-Blind Treatment Phase LTG XR Arm, respectively.

[3] Baseline measures are on the Intent-to-Treat (ITT) Population, participants who took at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. Four and six participants did not meet the ITT definition in the Double-Blind Treatment Phase Placebo Arm and the Double-Blind Treatment Phase LTG XR Arm, respectively.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percent Change From Baseline in Weekly Primary Generalized Tonic-clonic (PGTC) Seizure Frequency During the Entire Double-Blind Treatment Phase
Measure Description	Percent change from baseline is calculated as the number of seizures by week during the Double-Blind Treatment Phase (Treatment Week 1 up to Week 19) compared to the number of seizures per week during the Baseline Phase (Baseline Week 1 up to Week 8). A positive number equals a reduction in seizure frequency. PGTC seizures are more commonly known as gran mal seizures.
Time Frame	Baseline through end of Double-Blind Treatment Phase (up to Week 19)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants who took at least one dose of study drug and had at least one post-baseline efficacy assessment in the Double-Blind Treatment Phase. One participant in each treatment group did not have any PGTC seizures during the Baseline Phase.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	72	69
Percent Change From Baseline in Weekly Primary Generalized Tonic-clonic (PGTC) Seizure Frequency During the Entire Double-Blind Treatment Phase [units: percent change] Median (Full Range)	32.1 (-427 to 100)	75.4 (-100 to 100)

Statistical Analysis 1 for Percent Change From Baseline in Weekly Primary Generalized Tonic-clonic (PGTC) Seizure Frequency During the Entire Double-Blind Treatment Phase

Groups	Double-Blind Phase: Placebo, Double-Blind Phase: LTG XR
Method	Cochran-Mantel-Haenszel
P-Value	<0.0001
Median Difference (Final Values)	31.6
95% Confidence Interval	15.8 to 48.1

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction in PGTC Seizure Frequency During the Entire Double-Blind (DB)Treatment Phase (TP), the Escalation Phase, the Maintenance Phase, and the Last 8 Weeks of the Maintenance Phase
Measure Description	Change in seizure frequency was calculated as the average seizure frequency during each of the following: the Entire DB Treatment Phase (Treatment Week 1 up to Week 19); the Escalation Phase (Treatment Week 1 up to Week 7); the Maintenance Phase (Treatment Week 8 up to Week 19); and the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19), minus the seizure frequency at Baseline.
Time Frame	Entire DB Treatment Phase (Treatment Week 1 up to Week 19), Escalation Phase (Treatment Week 1 up to Week 7), Maintenance Phase (Treatment Week 8 up to Week 19), and the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19)
Safety Issue?	No

Analysis Population Description

ITT Population. One participant in each treatment group did not have any PGTC seizures during the Baseline Phase, as a result they were not counted in this efficacy endpoint; an additional 2 and 1 participants in the Placebo and LTG XR group, respectively, were not counted in the Maintenance Phase (MP) or last 8 weeks of MP due to study withdrawal.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	72	69
Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction in PGTC Seizure Frequency During the Entire Double-Blind (DB)Treatment Phase (TP), the Escalation Phase, the Maintenance Phase, and the Last 8 Weeks of the Maintenance Phase [units: participants]		
>=25% reduction, Entire DB TP, n=72, 69	43	56
>=50% reduction, Entire DB TP, n=72, 69	23	48
>=75% reduction, Entire DB TP, n=72, 69	14	35
100% reduction, Entire DB TP, n=72, 69	7	14
>=25% reduction, Escalation Phase, n=72, 69	39	51
>=50% reduction, Escalation Phase, n=72, 69	23	38
>=75% reduction, Escalation Phase, n=72, 69	14	24
100% reduction, Escalation Phase, n=72, 69	9	15
>=25% reduction, Maintenance Phase,	46	60

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
n=70, 68		
>=50% reduction, Maintenance Phase, n=70, 68	29	51
>=75% reduction, Maintenance Phase, n=70, 68	14	40
100% reduction, Maintenance Phase, n=70, 68	10	31
>=25% reduction, Last 8 Weeks of MP, n=70, 68	47	61
>=50% reduction, Last 8 Weeks of MP, n=70, 68	29	54
>=75% reduction, Last 8 Weeks of MP, n=70, 68	18	44
100% reduction, Last 8 Weeks of MP, n=70, 68	15	35

3. Secondary Outcome Measure:

Measure Title	Percent Change From Baseline in PGTC Seizure Frequency During the Escalation Phase, the Maintenance Phase, and During the Last 8 Weeks of the Maintenance Phase of the Double-Blind Treatment Phase
Measure Description	Percent change from baseline is calculated as the number of seizures by week during the Escalation Phase (Treatment Week 1 up to Week 7), the Maintenance Phase (Treatment Week 8 up to Week 19), and

	during the last 8 weeks of the Maintenance Phase (Treatment Week 12 up to Week 19) compared to the number of seizures per week during the Baseline Phase (Baseline Week 1 up to Week 8). A positive number equals a reduction in seizure frequency.
Time Frame	Escalation Phase (Treatment Week 1 up to Week 7), Maintenance Phase (Treatment Week 8 up to Week 19), and the last 8 weeks of the Maintenance Phase (Week 12 up to Week 19)
Safety Issue?	No

Analysis Population Description

ITT Population. One participant in each treatment group did not have any PGTC seizures during the Baseline Phase as a result they were not counted for this efficacy endpoint; an additional 2 and 1 participants in the Placebo and LTG XR group, respectively, were not counted in the Maintenance Phase (MP) or last 8 weeks of MP due to study withdrawal.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	72	69
Percent Change From Baseline in PGTC Seizure Frequency During the Escalation Phase, the Maintenance Phase, and During the Last 8 Weeks of the Maintenance Phase of the Double-Blind		

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Treatment Phase [units: percent change] Median (Full Range)		
Escalation Phase, n=72, 69	30.6 (-319 to 100)	61.9 (-197 to 100)
Maintenance Phase, n=70, 68	33.3 (-492 to 100)	89.7 (-142 to 100)
Last 8 weeks of the Maintenance Phase, n=70, 68	35.4 (-180 to 100)	100.0 (-131 to 100)

4. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Time to >=50% Reduction in Seizure Frequency in the Double-Blind Treatment Phase
Measure Description	50% reduction in seizure frequency is defined as the time at which a participant first achieved and maintained a >=50% reduction in seizure frequency following exposure to at least 1 week of study drug.
Time Frame	Baseline through end of Double-Blind Treatment Phase (up to Week 19)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	73	70
Number of Participants With the Indicated Time to >=50% Reduction in Seizure Frequency in the Double-Blind Treatment Phase [units: participants]		
2 weeks	12	22
4 weeks	12	28
8 weeks	14	39
12 weeks	20	43
16 weeks	23	48

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in Body Weight at Week 19 of the Double-Blind Treatment Phase
Measure Description	Change from baseline in body weight is calculated as the Week 19 (or last on-study measurement in Double-Blind Treatment Phase) value

	minus the Baseline value.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	73	70
Change From Baseline in Body Weight at Week 19 of the Double-Blind Treatment Phase [units: kilograms] Median (Full Range)	1.00 (-7.7 to 10.0)	0.00 (-11.4 to 8.8)

6. Secondary Outcome Measure:

Measure Title	Number of Participants With Improved Clinical Status on the Investigator's Global Assessment in the Double-Blind

	Treatment Phase
Measure Description	The investigators rated the participants' overall clinical status based on 7 clinical factors and an overall factor: seizure frequency, duration, and intensity; adverse experiences; social, intellectual, and motor functioning. Using a 7-point scale (marked deterioration [1], moderate deterioration [2], mild deterioration [3], no change [4], mild improvement [5], moderate improvement [6], or marked improvement [7]), the investigators assessed the participants' status compared to their condition prior to initiating study medication.
Time Frame	Week 19 (or last on-study assessment in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. Overall clinical status not assessed for 2 participants in each of the Placebo and LTG XR groups, respectively.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	71	68
Number of Participants With Improved Clinical Status on the Investigator's Global Assessment in the Double-Blind		

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Treatment Phase [units: participants]		
Any improvement, score of 5-7	36	57
No change, score of 4	33	10
Any deterioration, score of 1-3	2	1

7. Secondary Outcome Measure:

Measure Title	Number of Participants With Improved Satisfaction With Seizure Control on the Subject Satisfaction Questionnaire in the Double-Blind Treatment Phase
Measure Description	Participants were asked to rate their satisfaction with their seizure control compared to their seizure control prior to initiating study drug on a 7 point scale: marked deterioration (1), moderate deterioration (2), mild deterioration (3), no change (4), mild improvement (5), moderate improvement (6), or marked improvement (7).
Time Frame	Week 19 (or last on-study assessment in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. Participant satisfaction was not assessed for 2 participants in each of the Placebo and LTG XR groups, respectively.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	71	68
Number of Participants With Improved Satisfaction With Seizure Control on the Subject Satisfaction Questionnaire in the Double-Blind Treatment Phase [units: participants]		
Any improvement, score of 5-7	53	60
No change, score of 4	13	6
Any deterioration, score of 1-3	5	2

8. Secondary Outcome Measure:

Measure Title	Percent Change From Baseline in Weekly PGTC Seizure Frequency During the Entire Continuation Phase (CP), the Transition Phase, the Open-Label Phase, and the Last 8 Weeks of the Open-Label Phase
Measure Description	Percent change from baseline is calculated as the number of seizures by week during the entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase

	(CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52) minus the number of seizures per week during the Baseline Phase (Baseline Week 1 through Week 8). A positive number equals a reduction in seizure frequency.
Time Frame	Entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase (CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52)
Safety Issue?	No

Analysis Population Description

ITT Population for CP: all participants who took at least one dose of study medication during the CP and had at least one post baseline seizure assessment during the CP. Variability in participant numbers are due to not having any PGTC seizures during the Baseline Phase and study withdrawal prior to progressing to the next phase.

Reporting Groups

	Description
Continuation Phase: Placebo/LTG	Placebo participants who entered the CP
Continuation Phase: LTG/LTG	LTG XR participants who entered the CP
Baseline Failures	Baseline failures who entered the CP

Measured Values

	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Number of Participants Analyzed	68	66	24
Percent Change From Baseline in Weekly PGTC Seizure Frequency During the			

	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Entire Continuation Phase (CP), the Transition Phase, the Open-Label Phase, and the Last 8 Weeks of the Open-Label Phase [units: percent change] Median (Full Range)			
Entire Continuation Phase, n=68, 66, 24	85.2 (-113.3 to 100.0)	95.1 (-100.0 to 100.0)	21.7 (-115.4 to 100.0)
Transition Phase, n=68, 66, 20	73.1 (-90.5 to 100.0)	100.0 (-100.0 to 100.0)	100.0 (-100.0 to 100.0)
Open-Label Phase, n=68, 64, 23	89.2 (-116.7 to 100.0)	95.0 (-100.0 to 100.0)	31.7 (-194.7 to 100.0)
Last 8 weeks of Open-Label Phase, n=68, 63, 19	100.0 (-184.2 to 100.0)	100.0 (-53.3 to 100.0)	100.0 (-500.0 to 100.0)

9. Secondary Outcome Measure:

Measure Title	Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction or >=50% Increase From Baseline in Weekly PGTC Seizure Frequency for the Entire Continuation Phase, the Transition Phase, the Open-Label (OL) Phase, and the Last 8 Weeks of the OL Phase.
Measure Description	Change in seizure frequency was calculated as the average seizure frequency during each of the following: the Entire CP (CP Week 1 up to Week 52); the Transition Phase (CP Week 1 up to Week 7); the Open-Label (OL) Phase (CP Week 8 up to Week 52); and the last 8 weeks of the Open Label Phase (CP Week 45 up to Week 52) minus

	the seizure frequency at Baseline. W, Week.
Time Frame	Entire CP (CP Week 1 up to Week 52), the Transition Phase (CP Week 1 up to Week 7), the Open-Label Phase (CP Week 8 up to Week 52), and the last 8 weeks of the Open-Label Phase (CP Week 45 up to Week 52)
Safety Issue?	No

Analysis Population Description

ITT Population for CP. Variability in participant numbers are due to not having any PGTC seizures during the Baseline Phase and study withdrawal prior to progressing to the next phase.

Reporting Groups

	Description
Continuation Phase: Placebo/LTG	Placebo participants who entered the CP
Continuation Phase: LTG/LTG	LTG XR participants who entered the CP
Baseline Failures	Baseline failures who entered the CP

Measured Values

	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Number of Participants Analyzed	68	66	24
Number of Participants With >=25%, >=50%, >=75%, or 100% Reduction or >=50% Increase From Baseline in Weekly PGTC Seizure Frequency for the Entire Continuation Phase, the Transition Phase, the Open-Label (OL) Phase, and the Last			

	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
8 Weeks of the OL Phase. [units: participants]			
>=25% reduction, Entire CP, n=68, 66, 24	59	63	11
>=50% reduction, Entire CP, n=68, 66, 24	57	59	11
>=75% reduction, Entire CP, n=68, 66, 24	46	49	8
100% reduction, Entire CP, n=68, 66, 24	16	28	6
>=50% increase, Entire CP, n=68, 66, 24	2	1	10
>=25% reduction, Transition Phase, n=68, 66, 20	51	60	13
>=50% reduction, Transition Phase, n=68, 66, 20	44	56	12
>=75% reduction, Transition Phase, n=68, 66, 20	33	46	12
100% reduction, Transition Phase, n=68, 66, 20	27	41	12
>=50% increase, Transition Phase, n=68, 66, 20	3	1	3
>=25% reduction, Open-Label Phase, n=68, 64, 23	61	61	12
>=50% reduction, Open-Label Phase,	56	57	10

	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
n=68, 64, 23			
>=75% reduction, Open-Label Phase, n=68, 64, 23	47	49	8
100% reduction, Open-Label Phase, n=68, 64, 23	21	28	6
>=50% increase, Open-Label Phase, n=68, 64, 23	2	1	10
>=25% reduction, Last 8 W of OL Phase,n=68, 63, 19	60	60	10
>=50% reduction, Last 8 W of OL Phase,n=68, 63, 19	53	53	10
>=75% reduction, Last 8 W of OL Phase,n=68, 63, 19	45	47	10
100% reduction, Last 8 W of OL Phase, n=68, 63, 19	35	41	10
>=50% increase, Last 8 W of OL Phase, n=68, 63, 19	2	1	4

10. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Profile of Mood State (POMS) Mood Disturbance Total Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The POMS is a self-administered 65-item questionnaire that evaluates the participants' perception of their mood state in 6 areas:

	tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely), with higher scores indicating a more negative mood state. A total score (from 0 to 24) is obtained by summing the scores of the six domains.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 53 and 57 participants in the Placebo and LTG XR groups, respectively. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	20	13
Mean Change From Baseline in the Profile of Mood State (POMS) Mood Disturbance Total Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	2.4 (6.97)	9.7 (8.65)

11. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Center for Epidemiological Studies-Depression Scale (CES-D) Total Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The 20-item CES-D questionnaire is self-administered and asks respondents to report the frequency to which the 20 events were experienced over the past week. A 4-point Likert scale is used and ranges from rarely or none of the time (0) to most or all of the time (3). The total score, a sum across the 20 items (ranging from 0 to 60), determines the extent to which a participant may be experiencing depression. Higher scores indicate a higher severity of depression.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 64 and 59 participants in the Placebo and LTG XR groups, respectively. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	9	11
Mean Change From Baseline in the Center for Epidemiological Studies-Depression Scale (CES-D) Total Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	2.9 (2.81)	2.4 (2.54)

12. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) 6-Item Total Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The NDDI-E is a self-reported questionnaire composed of 46 brief phrases/words to identify mood disorders across the spectrum of depression. It was developed to capture depressive moods that are co-morbid with the disease of epilepsy or its treatment as well as to measure the depressive state of the participant. All phrases are measured on a 4-point Likert scale of Never (1) to Always/often (4) and refer to the participants' mood over the past week. Scoring is comprised of a total mood score calculated by summing the scores of 6 specific items (from 6=never to 24=always or often).
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 65 participants in both the Placebo and LTG XR groups. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	8	5
Mean Change From Baseline in the Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) 6-Item Total Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	-0.1 (0.98)	-2.4 (1.24)

13. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Quality of Life in Epilepsy-31-P (QOLIE-31P) Overall Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The QOLIE-31 is a 31-item questionnaire that evaluates the participants' perception of his or her quality of life in 7 domains: seizure worry, emotional well being, energy/fatigue, cognitive functioning,

	medication effects, social functioning, and overall quality of life. Each domain (with scores ranging from 0 to 100) is summed and divided by the total number of questions that were answered. The overall score is derived by weighting and then summing up the seven domain scores.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 55 participants in both the Placebo and LTG XR groups. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	18	15
Mean Change From Baseline in the Quality of Life in Epilepsy-31-P (QOLIE-31P) Overall Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	-6.5 (3.97)	-8.5 (4.35)

14. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Adverse Experience Profile (AEP) Total Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The AEP is a list of 19 items covering many possible side effects attributable to drug treatment. The participants respond by assessing how much each event has been a problem for them over the past 4 weeks (1=Never a Problem to 4=Always a Problem). Each individual item can be examined; an overall adverse events score is calculated as the sum of the scores across the 19 items. The AEP total score ranges from 19 to 76, with a higher score indicating a higher degree of adverse event severity.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 65 participants in both the Placebo and LTG XR groups. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	8	5
Mean Change From Baseline in the Adverse Experience Profile (AEP) Total Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	3.0 (2.16)	1.4 (2.77)

15. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Seizure Severity Questionnaire (SSQ) Global Bother Score at Week 19 Double-Blind Treatment Phase
Measure Description	The SSQ is a self-reported instrument developed to assess the severity of seizures and seizure symptoms. The scale consists of 10 major clinical features/symptoms of seizures that the participants rate on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]). The Global Bother Domain is the primary score used for the analysis of the SSQ and has scores ranging from 1 to 7.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 68 and 67 participants in the Placebo and LTG XR groups, respectively. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	5	3
Mean Change From Baseline in the Seizure Severity Questionnaire (SSQ) Global Bother Score at Week 19 Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	0.86 (0.84)	1.23 (1.08)

16. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in the Epworth Sleepiness Scale (ESS) 8-Item Total Score at Week 19 of the Double-Blind Treatment Phase
Measure Description	The ESS is an 8-item, self-administered questionnaire that measures excessive daytime sleepiness in adults. The instrument captures information on the extent to which the participant would be likely, or not, to fall asleep in certain situations. The stimulus question is: How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Questions are answered on a 4-point scale (would never doze [0] to high chance of dozing [3]). The total

	score ranges from 0 to 24, where a higher score indicates a higher chance of dozing.
Time Frame	Baseline and Week 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

ITT Population. The questionnaire was not completed by 55 and 51 participants in the Placebo and LTG XR groups, respectively. Only participants completing the questionnaire were included in the analysis of this outcome measure.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	18	19
Mean Change From Baseline in the Epworth Sleepiness Scale (ESS) 8-Item Total Score at Week 19 of the Double-Blind Treatment Phase [units: points on a scale] Least Squares Mean (Standard Error)	-0.6 (0.69)	1.0 (0.67)

17. Secondary Outcome Measure:

Measure Title	Serum Concentrations and Population (POP) Pharmacokinetic Parameters for Lamotrigine
Measure Description	Serum samples for participants on lamotrigine were analyzed with a validated analytical method based on solid phase extraction of serum followed by High-Performance Liquid Chromatography (HPLC) Mass Spectrometry (MS)/MS analysis. The lower limit of quantification (LLQ) for serum lamotrigine was 4 nanograms (ng)/milliliter (mL), using a 50 microliter (µL) aliquot of human serum with a higher limit of quantification (HLQ) of 4,000 ng/mL. PK data cannot be reported, as PK data from several different studies have been combined into one POP/PK analysis and cannot be separated by study.
Time Frame	Blood samples drawn at Treatment Weeks 11, 15, and 19 (or last on-study measurement in Double-Blind Treatment Phase)
Safety Issue?	No

Analysis Population Description

PK Population: Number of participants analyzed for PK data cannot be reported, as PK data from several different studies have been combined into one POP/PK analysis and cannot be separated by study.

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	LTG XR once daily

Measured Values

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

Reported Adverse Events

Reporting Groups

	Description
Double-Blind Phase: Placebo	Control - matching placebo once daily
Double-Blind Phase: LTG XR	Lamotrigine (LTG) extended release (XR) once daily
Continuation Phase: Placebo/LTG	Participants who received placebo in the Double-Blind Phase and then entered the CP, in which they received LTG
Continuation Phase: LTG/LTG	Participants who received LTG XR in the Double-Blind Phase and then entered the CP, in which they received LTG
Baseline Failures	Baseline failures who entered the CP without receiving treatment in the Double-Blind Phase. Baseline Failures were participants that successfully progressed through the Screening Phase and completed the Baseline Phase of the Double-blind Study, but ultimately did not meet the seizure frequency criteria for randomization into the Double-Blind Treatment Phase of the study. As a result, they were not counted as having started in the Double-Blind Study, but were eligible to enter the CP of the study.

Additional Description

Serious adverse events (SAEs) and adverse events (AEs) were collected for all participants in the Safety Population. The Safety Population was defined as all participants who took at least one dose of study drug.

Serious Adverse Events

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Total # participants affected/at risk	0/74 (0%)	1/72 (1.39%)	3/69 (4.35%)	3/67 (4.48%)	1/32 (3.12%)
Gastrointestinal disorders					
Abdominal pain † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					
Nausea † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					
Vomiting † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Bile duct cancer † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	0/32 (0%)

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
# events					
Uterine leiomyoma † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	1/67 (1.49%)	0/32 (0%)
# events					
Nervous system disorders					
Altered state of consciousness † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	0/32 (0%)
# events					
Ataxia † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					
Hemiparesis † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	0/32 (0%)
# events					
Hydrocephalus † [A]					
# participants affected/at	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	0/32 (0%)

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
risk					
# events					
Nystagmus † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					
Syncope vasovagal † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	1/67 (1.49%)	0/32 (0%)
# events					
Pregnancy, puerperium and perinatal conditions					
Abortion spontaneous † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	1/67 (1.49%)	0/32 (0%)
# events					
Psychiatric disorders					
Confusional state † [A]					
# participants affected/at risk	0/74 (0%)	1/72 (1.39%)	0/69 (0%)	0/67 (0%)	0/32 (0%)
# events					
Conversion disorder † [A]					

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
# participants affected/at risk	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	0/32 (0%)
# events					
Suicide attempt † [A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	0/69 (0%)	0/67 (0%)	1/32 (3.12%)
# events					

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
Total # participants affected/at risk	21/74 (28.38%)	27/72 (37.5%)	29/69 (42.03%)	21/67 (31.34%)	18/32 (56.25%)
Eye disorders					
Diplopia † [A]					
# participants affected/at risk	1/74 (1.35%)	4/72 (5.56%)	4/69 (5.8%)	1/67 (1.49%)	2/32 (6.25%)
# events					
Vision blurred † [A]					
# participants affected/at	0/74 (0%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	2/32 (6.25%)

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
risk					
# events					
Gastrointestinal disorders					
Abdominal pain † [A]					
# participants affected/at risk	3/74 (4.05%)	0/72 (0%)	1/69 (1.45%)	0/67 (0%)	2/32 (6.25%)
# events					
Diarrhoea † [A]					
# participants affected/at risk	0/74 (0%)	1/72 (1.39%)	3/69 (4.35%)	1/67 (1.49%)	2/32 (6.25%)
# events					
Nausea † [A]					
# participants affected/at risk	4/74 (5.41%)	5/72 (6.94%)	1/69 (1.45%)	1/67 (1.49%)	5/32 (15.62%)
# events					
Vomiting † [A]					
# participants affected/at risk	3/74 (4.05%)	7/72 (9.72%)	5/69 (7.25%)	2/67 (2.99%)	2/32 (6.25%)
# events					
General disorders					
Fatigue † [A]					

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
# participants affected/at risk	2/74 (2.7%)	1/72 (1.39%)	1/69 (1.45%)	0/67 (0%)	3/32 (9.38%)
# events					
Pain †[A]					
# participants affected/at risk	2/74 (2.7%)	2/72 (2.78%)	3/69 (4.35%)	2/67 (2.99%)	2/32 (6.25%)
# events					
Pyrexia †[A]					
# participants affected/at risk	4/74 (5.41%)	5/72 (6.94%)	7/69 (10.14%)	5/67 (7.46%)	3/32 (9.38%)
# events					
Infections and infestations					
Nasopharyngitis †[A]					
# participants affected/at risk	1/74 (1.35%)	2/72 (2.78%)	4/69 (5.8%)	4/67 (5.97%)	2/32 (6.25%)
# events					
Nervous system disorders					
Ataxia †[A]					
# participants affected/at risk	0/74 (0%)	0/72 (0%)	2/69 (2.9%)	2/67 (2.99%)	2/32 (6.25%)

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
# events					
Dizziness †[A]					
# participants affected/at risk	5/74 (6.76%)	4/72 (5.56%)	7/69 (10.14%)	4/67 (5.97%)	7/32 (21.88%)
# events					
Headache †[A]					
# participants affected/at risk	12/74 (16.22%)	10/72 (13.89%)	11/69 (15.94%)	5/67 (7.46%)	9/32 (28.12%)
# events					
Somnolence †[A]					
# participants affected/at risk	0/74 (0%)	1/72 (1.39%)	1/69 (1.45%)	2/67 (2.99%)	2/32 (6.25%)
# events					
Tremor †[A]					
# participants affected/at risk	0/74 (0%)	4/72 (5.56%)	5/69 (7.25%)	3/67 (4.48%)	3/32 (9.38%)
# events					
Skin and subcutaneous tissue disorders					
All rash †[A]					
# participants affected/at risk	4/74 (5.41%)	2/72 (2.78%)	2/69 (2.9%)	1/67 (1.49%)	2/32 (6.25%)

	Double-Blind Phase: Placebo	Double-Blind Phase: LTG XR	Continuation Phase: Placebo/LTG	Continuation Phase: LTG/LTG	Baseline Failures
# events					

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response Center

Organization: GlaxoSmithKline

Phone: 866-435-7343

Email: