Clinical trial results:
Clinical Evaluation of lamotrigine in Epilepsy-Mutual Recognition-D2012-6595-Study only identified as requiring Article 46 submission-30 July 2012 (as part of r/co-administration retrospective exercise)

Summary

EudraCT number	2015-004901-18
Trial protocol	Outside EU/EEA
Global end of trial date	26 March 2009

Results information

Result version number	v1 (current)
This version publication date	23 December 2016
First version publication date	23 December 2016

Trial information

Trial identification

Sponsor protocol code	LAM107844

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2009
Global end of trial reached?	Yes
Global end of trial date	26 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 102
Worldwide total number of subjects	102
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	35
Adolescents (12-17 years)	22
Adults (18-64 years)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 102 participants were enrolled in the study. Of these, 99 participants completed the maintenance phase, and 97 participants entered the continuation phase.

Period 1

Period 1 title	Escalation Phase + Maintenance Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adults: LTG

Arm description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Arm type	Experimental
Investigational medicinal product name	BW430C (Lamotrigine) 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Arm title	Adolescents: LTG

Arm description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Arm type	Experimental
Investigational medicinal product name	BW430C (Lamotrigine) 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Number of subjects in period 1	Adults: LTG	Adolescents: LTG
Started	51	51
Completed	50	49
Not completed	1	2
Adverse event, non-fatal	1	2

Period 2

Period 2 title	Continuation Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adults: LTG

Arm description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Arm type	Experimental
Investigational medicinal product name	BW430C (Lamotrigine) 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and

adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Arm title	Adolescents: LTG

Arm description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Arm type	Experimental
Investigational medicinal product name	BW430C (Lamotrigine) 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Investigational medicinal product name	BW430C (Lamotrigine) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

Number of subjects in period 2[1]	Adults: LTG	Adolescents: LTG
Started	49	48
Completed	34	35
Not completed	15	13
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	-
Withdrawal Due to Wishes of Family	1	-
Poor Compliance	1	-
Lack of efficacy	12	11

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 99 participants (50 adults and 49 children) completed the maintenance phase. Of these, 97 participants (49 adults and 48 children) entered the continuation phase and 2 participants (1 adult and 1 child) discontinued the study due to lack of efficacy.

Baseline characteristics

Reporting groups	
Reporting group title	Adults: LTG

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Reporting group title	Adolescents: LTG

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Reporting group values	Adults: LTG	Adolescents: LTG	Total
Number of subjects	51	51	102
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29	8.2	
standard deviation	± 9.9	± 4.1	-
Gender categorical Units: Subjects			
Female	23	25	48
Male	28	26	54
Race/Ethnicity, Customized Units: Subjects			
Asian–Japanese	51	51	102

End points

End points reporting groups

Reporting group title	Adults: LTG

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Reporting group title	Adolescents: LTG

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Reporting group title	Adults: LTG

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Reporting group title	Adolescents: LTG

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Subject analysis set title	Total: LTG
Subject analysis set type	Full analysis

Subject analysis set description:

Adult participants were initiated on 12.5 mg/day, and adolescents were initiated on 0.15 mg/kg/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking VPA or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. During the MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Primary: Number of participants with any rash event (including Stevens–Johnson syndrome [SJS] and any other serious drug eruption) during the initial 8 weeks of study treatment

End point title	Number of participants with any rash event (including Stevens–Johnson syndrome [SJS] and any other serious drug eruption) during the initial 8 weeks of study treatment

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

Safety Population: all participants enrolled in the study who received at least one dose of study medication

End point type	Primary

End point timeframe:

8 weeks

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	51[1]	51[2]	102[3]	
Units: participants	2	3	5	

Notes:

[1] - Safety Population

[2] - Safety Population

[3] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The estimated value represents the percentage of participants with rash events.

Comparison groups	Adults: LTG v Adolescents: LTG v Total: LTG
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage of participants
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	11.1

Primary: Number of participants with any rash event (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point title	Number of participants with any rash event (including SJS and

	any other serious drug eruption) up to the end of the maintenance phase[4]

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

End point type	Primary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	51[5]	51[6]	102[7]	
Units: participants	2	3	5	

Notes:

[5] - Safety Population

[6] - Safety Population

[7] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of rash events experienced (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point title	Number of rash events experienced (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

End point type	Secondary

End point timeframe:

8 weeks

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2[8]	3[9]	5[10]	
Units: rash events	3	4	7	

Notes:

[8] - Safety Population

[9] - Safety Population

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point title	Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point description:

The rash events (including SJS and any other serious drug eruption) were classified into severe (rash prevents participant from leading a normal life), moderate (participant's discomfort due to rash interferes with daily life), and mild (no interference with participant's daily life due to rash), based on the intesity of the event.

End point type	Secondary

End point timeframe:

8 weeks

End point values	Total: LTG			
Subject group type	Subject analysis set			
Number of subjects analysed	5[11]			
Units: participants				
Severe	0			
Moderate	2			
Mild	3			

Notes:

[11] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of drug-related and not related rash events (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point title	Number of drug-related and not related rash events (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

End point description:

The adverse event of rash was considered to be drug-related when the Investigator answered "Yes" to the following question: "Is there a reasonable possibility that the adverse event may have been caused by the investigational product?".

End point type	Secondary

End point timeframe:

8 weeks

End point values	Total: LTG			
Subject group type	Subject analysis set			
Number of subjects analysed	5[12]			
Units: rash events				
Drug related	3			
Not related to drug	4			

Notes:

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least a 50 percent reduction in seizure frequency for the indicated types of seizures

End point title	Percentage of participants with at least a 50 percent reduction in seizure frequency for the indicated types of seizures

End point description:

Partial seizures are seizures that affect only a part of the brain at onset. Tonic-clonic seizures (grand mal seizures) affect the entire brain and are characterized by a generalized involuntary muscular contraction and cessation of respiration followed by tonic and clonic spasms of the muscles. Lennox-Gastaut syndrome (LGS) is a pediatric epilepsy syndrome characterized by multiple seizure types; mental retardation or regression; and abnormal findings on an electroencephalogram (EEG), with paroxysms of fast activity and generalized slow spike-and-wave discharges.

Full Analysis Set (FAS) Population: all enrolled participants except those who had no assessments of the main efficacy variable (percent reduction in seizure frequency).

End point type	Secondary

End point timeframe:

8 weeks

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28[13]	25[14]	53[15]	
Units: percentage of participants				
number (not applicable)				
All Partial Seizures, n=28, 25, 53	17.9	20	18.9	
Tonic-clonic Seizures, n=5, 4, 9	60	0	33.3	
Generalized Seizures with LGS, n=25, 25, 50	16	20	18	

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in seizure frequency of the indicated types of seizures

End point title	Percent change in seizure frequency of the indicated types of seizures

End point description:

Percent change in seizure frequency was calculated as 100 * (pre-treatment seizures minus MP seizures)/pre-treatment seizures. Partial seizures are seizures that affect only a part of the brain at onset. Tonic-clonic seizures (grand mal seizures) affect the entire brain and are characterized by a generalized involuntary muscular contraction and cessation of respiration followed by tonic and clonic spasms of the muscles. Lennox-Gastaut syndrome (LGS) is a pediatric epilepsy syndrome characterized by multiple seizure types, mental retardation or regression, and abnormal findings on an ECG.

End point type	Secondary

End point timeframe:

Pre-treatment (Day 0) and Week 8 of the Maintenance Phase (Study Week 14)

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28[16]	25[17]	53[18]	
Units: percent change				
median (confidence interval 95%)				
All Partial Seizures, n=28, 25, 53	6.3 (-44.8 to 28.7)	-11.1 (-46.6 to 34.6)	-9.8 (-42.3 to 28.6)	
Tonic-clonic Seizures, n=5, 4, 9	83.3 (-99999 to 99999)	27.4 (-99999 to 99999)	36.5 (-47.9 to 100)	
Generalized Seizures with LGS, n=25, 25, 50	18.6 (-16.2 to 32.2)	10.1 (-24.9 to 28.8)	12.4 (5.8 to 27.6)	

Notes:

[16] - FAS Population

[17] - FAS Population

[18] - FAS Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of rash events experienced (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point title	Number of rash events experienced (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

Safety Population. Only those participants who had experienced any rash event were evaluated.

End point type	Secondary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2[19]	3[20]	5[21]	
Units: rash events	3	4	7	

Notes:

[19] - Safety Population

[20] - Safety Population

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point title	Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point description:

The rash events (including SJS and any other serious drug eruption) were classified into severe (rash prevents participant from leading a normal life), moderate (participant's discomfort due to rash interferes with daily life), and mild (no interference with participant's daily life due to rash), based on the intesity of the event.

End point type	Secondary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

End point values	Total: LTG			
Subject group type	Subject analysis set			
Number of subjects analysed	5[22]			
Units: participants				
Severe	0			
Moderate	2			
Mild	3			

Notes:

[22] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of drug-related and not related rash events (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point title	Number of drug-related and not related rash events (including SJS and any other serious drug eruption) up to the end of the maintenance phase

End point description:

The adverse event of rash was considered to be drug-related when the Investigator answered "Yes" to the following question: "Is there a reasonable possibility that the adverse event may have been caused by the investigational product?".

End point type	Secondary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

End point values	Total: LTG			
Subject group type	Subject analysis set			
Number of subjects analysed	5[23]			
Units: rash events				
Drug related	3			
Not related to drug	4			

Notes:

[23] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of rash events (including SJS and any other serious drug eruption) adjudicated by the rash adjudication committee in participants taking VPA

End point title	Number of rash events (including SJS and any other serious drug eruption) adjudicated by the rash adjudication committee in participants taking VPA

End point description:

The rash adjudication committee reviewed all rash events from a dermatologic standpoint based on the nature, onset site, affected area, time to onset, outcome, and the investigator's comments to adjudicate whether or not the reported event was a drug eruption. A drug eruption is an eruption or a solitary lesion caused by a drug taken internally, often a result of allergic sensitization.

End point type	Secondary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

End point values	Adults: LTG	Adolescents: LTG	Total: LTG	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2[24]	3[25]	5[26]	
Units: adjudicated rash events	1	2	3	

Notes:

[24] - Safety Population

[25] - Safety Population

[26] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with monocyte values outside the normal range (shifted high) at Weeks 4 and 8

End point title	Percentage of participants with monocyte values outside the normal range (shifted high) at Weeks 4 and 8

End point description:

Monocytes are a type of white blood cell (WBC; typically comprising 2%-8% of total WBCs) and are a part of the immune system. The normal range for adults is 0.2 to 0.95 * 10^3 cells per microliter (µL); the normal range for adolescents is 0 to 0.8 * 10^3 cells per µL. The monocyte count may increase during chronic inflammation, stress response, immune-mediated disease, viral fever, etc. The percentage of participants (par.) with monocyte values outside the normal range was calculated as 100 * (number of par. with monocyte values outside the normal range) divided by the total number of par.

End point type	Secondary

End point timeframe:

Week 4 and Week 8

End point values	Total: LTG			
Subject group type	Subject analysis set			
Number of subjects analysed	102[27]			
Units: percentage of participants				
number (not applicable)				
Week 4	15.2			
Week 8	16.2			

Notes:

[27] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First day of study drug administration and the end of the maintenance phase-Week 8.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Adults: LTG

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproeic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

Reporting group title	Total: LTG

Reporting group description:

Adult participants were initiated on 12.5 mg/day, and adolescents were initiated on 0.15 mg/kg/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking VPA or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. During the MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Reporting group title	Adolescents: LTG

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

Serious adverse events	Adults: LTG	Total: LTG	Adolescents: LTG
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	7 / 102 (6.86%)	2 / 51 (3.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Therapeutic agent toxicity			

subjects affected / exposed	1 / 51 (1.96%)	1 / 102 (0.98%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 51 (1.96%)	1 / 102 (0.98%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 51 (1.96%)	1 / 102 (0.98%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 102 (0.98%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 102 (0.98%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 51 (1.96%)	1 / 102 (0.98%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 51 (0.00%)	1 / 102 (0.98%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 51 (1.96%)	1 / 102 (0.98%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adults: LTG	Total: LTG	Adolescents: LTG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 51 (72.55%)	83 / 102 (81.37%)	46 / 51 (90.20%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 51 (15.69%)	12 / 102 (11.76%)	4 / 51 (7.84%)
occurrences (all)	9	13	4
Arthropod sting			
subjects affected / exposed	1 / 51 (1.96%)	10 / 102 (9.80%)	9 / 51 (17.65%)
occurrences (all)	1	16	15
Excoriation			
subjects affected / exposed	6 / 51 (11.76%)	8 / 102 (7.84%)	2 / 51 (3.92%)
occurrences (all)	6	8	2
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 51 (11.76%)	17 / 102 (16.67%)	11 / 51 (21.57%)
occurrences (all)	9	20	11
Dizziness			
subjects affected / exposed	10 / 51 (19.61%)	12 / 102 (11.76%)	2 / 51 (3.92%)
occurrences (all)	11	13	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 51 (13.73%)	12 / 102 (11.76%)	5 / 51 (9.80%)
occurrences (all)	7	13	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 51 (5.88%)	14 / 102 (13.73%)	11 / 51 (21.57%)
occurrences (all)	3	16	13
Vomiting			

subjects affected / exposed	3 / 51 (5.88%)	10 / 102 (9.80%)	7 / 51 (13.73%)
occurrences (all)	3	13	10
Constipation			
subjects affected / exposed	3 / 51 (5.88%)	7 / 102 (6.86%)	4 / 51 (7.84%)
occurrences (all)	3	7	4
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	5 / 51 (9.80%)	20 / 102 (19.61%)	15 / 51 (29.41%)
occurrences (all)	6	27	21
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 51 (1.96%)	7 / 102 (6.86%)	6 / 51 (11.76%)
occurrences (all)	3	11	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 51 (19.61%)	24 / 102 (23.53%)	14 / 51 (27.45%)
occurrences (all)	12	33	21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported