Clinical trial results:
A multi-center, uncontrolled, open-label, evaluation of Lamotrigine monotherapy in newly diagnosed epilepsy or recurrent epilepsy (currently untreated)

Summary

EudraCT number	2015-004878-15
Trial protocol	Outside EU/EEA
Global end of trial date	24 October 2014

Results information

Result version number	v1 (current)
This version publication date	22 January 2017
First version publication date	22 January 2017

Trial information

Trial identification

Sponsor protocol code	115376

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	19 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2014
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	20 September 2011
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: 40
Country: Number of subjects enrolled	Korea, Republic of: 27
Worldwide total number of subjects	67
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)	0
Adolescents (12-17 years)	7
Adults (18-64 years)	47
From 65 to 84 years	12
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 70 participants were enrolled; 3 participants were screened but withdrew from the study before prescription of the first investigational product (67), and only 65 of the participants received at least one dose of the investigational product which comprised the safety population.

Pre-assignment

Screening details:

The study consisted of a 6-week Escalation Phase, a 24-week Maintenance Phase (MP), a >=2-week Taper Phase, and a post-study examination conducted within 1-4 weeks after the last dose of lamotrigine. In Japan only, the Extension Phase was conducted until either approval for this indication or after 24 months after Last Subject Last Visit in the MP.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lamotrigine

Arm description:

In the EP, lamotrigine 25 milligrams per day (mg/day) was orally administered once daily (QD; in the evening [PM]) as the initial dose from Week (W) 1 to W2. As a fixed dose escalation, lamotrigine 50 mg/day was orally administered QD (in the PM) from W3 to W4; 100 mg/day was administered from W5 to W6. In the MP, lamotrigine 200 mg/day was orally administered QD (in the PM) from W7 to W30. The dose could have been decreased to 100 mg/day per safety concerns. Per investigator discretion, the investigational product was discontinued if safety concerns remained. If the 200 mg/day dose did not control seizures, the dose could have been increased up to 400 mg/day by 50-100 mg/day at >=1-week intervals. A dose >200 mg/day could have been administered in 2 divided doses (in the morning and PM). In the ExP, lamotrigine was administered at 100-400 mg/day based on seizure status/safety. If a dose <100 or >400 mg/day was judged to be necessary, the participant was withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Lamotrigine tablets were administered once daily or twice daily.

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

Dosage and administration details:

Lamotrigine tablets were administered once daily or twice daily.

Number of subjects in period 1[1]	Lamotrigine
Started	65
Begin Escalation Phase (EP; 6 weeks)	65
Received Treatment	65
Complete EP (6 weeks)	52
Begin Maintenance Phase (MP; 24 weeks)	52
Complete MP (24 weeks)	42
Begin Extension Phase (ExP; >= 24weeks)	19 [2]
Complete ExP (>= 24 weeks)	19 [3]
Completed	32
Not completed	33
Physician decision	4
Consent withdrawn by subject	1
Adverse event, non-fatal	18
Protocol-defined Stopping Criteria	2
Lack of efficacy	7
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 70 participants were enrolled; 3 participants were screened but withdrew from the study before prescription of the first investigational product (67), and only 65 of the participants received at least one dose of the investigational product which comprised the safety population.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: In Japan only, the Extension Phase was conducted until either approval for this indication or after 24 months after Last Subject Last Visit in the MP.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: In Japan only, the Extension Phase was conducted until either approval for this indication or after 24 months after Last Subject Last Visit in the MP

Baseline characteristics

Reporting groups	
Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 25 milligrams per day (mg/day) was orally administered once daily (QD; in the evening [PM]) as the initial dose from Week (W) 1 to W2. As a fixed dose escalation, lamotrigine 50 mg/day was orally administered QD (in the PM) from W3 to W4; 100 mg/day was administered from W5 to W6. In the MP, lamotrigine 200 mg/day was orally administered QD (in the PM) from W7 to W30. The dose could have been decreased to 100 mg/day per safety concerns. Per investigator discretion, the investigational product was discontinued if safety concerns remained. If the 200 mg/day dose did not control seizures, the dose could have been increased up to 400 mg/day by 50-100 mg/day at >=1-week intervals. A dose >200 mg/day could have been administered in 2 divided doses (in the morning and PM). In the ExP, lamotrigine was administered at 100-400 mg/day based on seizure status/safety. If a dose <100 or >400 mg/day was judged to be necessary, the participant was withdrawn from the study.

Reporting group values	Lamotrigine	Total	
Number of subjects	65	65	
Age categorical Units: Subjects			
Age continuous			
Baseline data were collected in members of the Safety Population, comprised of all participants who had taken at least one dose of investigational product.			
Units: years			
arithmetic mean	37.3		
standard deviation	± 20.2	-	
Gender categorical			
Baseline data were collected in members of the Safety Population, comprised of all participants who had taken at least one dose of investigational product.			
Units: Subjects			
Female	26	26	
Male	39	39	
Race/Ethnicity, Customized			
Baseline data were collected in members of the Safety Population, comprised of all participants who had taken at least one dose of investigational product.			
Units: Subjects			
Asian - East Asian Heritage	26	26	
Asian - Japanese Heritage	39	39	

End points

End points reporting groups

Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 25 milligrams per day (mg/day) was orally administered once daily (QD; in the evening [PM]) as the initial dose from Week (W) 1 to W2. As a fixed dose escalation, lamotrigine 50 mg/day was orally administered QD (in the PM) from W3 to W4; 100 mg/day was administered from W5 to W6. In the MP, lamotrigine 200 mg/day was orally administered QD (in the PM) from W7 to W30. The dose could have been decreased to 100 mg/day per safety concerns. Per investigator discretion, the investigational product was discontinued if safety concerns remained. If the 200 mg/day dose did not control seizures, the dose could have been increased up to 400 mg/day by 50-100 mg/day at >=1-week intervals. A dose >200 mg/day could have been administered in 2 divided doses (in the morning and PM). In the ExP, lamotrigine was administered at 100-400 mg/day based on seizure status/safety. If a dose <100 or >400 mg/day was judged to be necessary, the participant was withdrawn from the study.

Primary: Number of participants who were seizure free in the Maintenance Phase (across seizure types and by seizure type within 6 months prior to the start of the study)

End point title	Number of participants who were seizure free in the Maintenance Phase (across seizure types and by seizure type within 6 months prior to the start of the study)[1]

End point description:

Participants were considered to be seizure free if they did not report any seizures during the Maintenance Phase. Seizure types are defined as: ALL=any type of seizure; A: simple partial seizures, B: complex partial seizures; C: partial seizures evolving to secondary generation seizures; D5: tonic-clonic seizures. Simple partial seizures are seizures that affect only a small region of the brain, often the temporal lobes or hippocampi. Complex partial seizures are epileptic seizures that are associated with bilateral cerebral hemisphere involvement and cause impairment of awareness or responsiveness. Partial seizures evolving to secondary generation seizures are seizures that start as partial seizures, then spread to include the entire brain. Tonic–clonic seizures are a type of generalized seizure that affects the entire brain.

End point type	Primary

End point timeframe:

Weeks 7 to 30

Notes:

[1] - 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	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	65[2]			
Units: participants				
All, n=65	28			
A+B+C, n=55	22			
A+B, n=42	17			
C, n=33	23			
D5, n=10	8			

Notes:

[2] - Full Analysis Set population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to withdrawal/dropout from the study (across seizure types and by seizure type in past 6 months in the Escalation and Maintenance Phases)

End point title	Time to withdrawal/dropout from the study (across seizure types and by seizure type in past 6 months in the Escalation and Maintenance Phases)

End point description:

Time to withdrawal is defined as the time from the start of treatment until withdrawal from the study. Seizure types are defined as: ALL=any type of seizure; A: simple partial seizures, B: complex partial seizures; C: partial seizures evolving to secondary generation seizures; D5: tonic-clonic seizures. Simple partial seizures are seizures which affect only a small region of the brain, often the temporal lobes or hippocampi. Simple partial seizures are seizures that affect only a small region of the brain, often the temporal lobes or hippocampi. Complex partial seizures are epileptic seizures that are associated with bilateral cerebral hemisphere involvement and cause impairment of awareness or responsiveness. Partial seizures evolving to secondary generation seizures are seizures that start as partial seizures, then spread to include the entire brain. Tonic–clonic seizures are a type of generalized seizure that affects the entire brain.

End point type	Secondary

End point timeframe:

up to Week 30

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	65[3]			
Units: Days				
arithmetic mean (standard error)				
All, n=65	150 (± 8.99)			
A+B+C, n=55	148.4 (± 9.72)			
A+B, n=42	147.9 (± 10.72)			
C, n=33	168 (± 10.91)			
D5, n=10	14.6 (± 0.54)			

Notes:

[3] - Full Analysis Set population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the first seizure in the Maintenance Phase (MP) (across seizure types and by seizure type)

End point title	Time to the first seizure in the Maintenance Phase (MP) (across seizure types and by seizure type)

End point description:

The time to the first seizure in the MP is measured at the time the first seizure occurred in the MP. Seizure types are defined as: ALL=any type of seizure; A: simple partial seizures, B: complex partial seizures; C: partial seizures evolving to secondary generation seizures; D5: tonic-clonic seizures. Simple partial seizures are seizures that affect only a small region of the brain, often the temporal lobes or hippocampi. Complex partial seizures are epileptic seizures that are associated with bilateral cerebral hemisphere involvement and cause impairment of awareness or responsiveness. Partial seizures evolving to secondary generation seizures are seizures that start as partial seizures, then spread to include the entire brain. Tonic–clonic seizures are a type of generalized seizure that affects the entire brain. 99999 indicates that data were not available; no participants had D5 seizures in the MP; thus,

mean time to the first D5 seizure in MP could not be calculated

End point type	Secondary

End point timeframe:

Weeks 7 to 30.

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	52[4]			
Units: Days				
arithmetic mean (standard error)				
All, n=52	103 (± 9.43)			
A+B+C, n=44	100.4 (± 10.44)			
A+B, n=34	94.2 (± 12.22)			
C, n=29	113.3 (± 12.06)			
D5, n=8	99999 (± 99999)			

Notes:

[4] - Full Analysis Set population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from study medication start until the end of treatment (up to Week 54).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who had taken at least one dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 25 mg/day was orally administered QD; in the evening(PM) as the initial dose from W1 to W2. As a fixed dose escalation, lamotrigine 50 mg/day was orally administered QD(in the PM) from W3 to W4; 100 mg/day was administered from W5 to W6. In the MP, Lamotrigine 200 mg/day was orally administered QD(PM) from W7 to W30. The dose could have been decreased to 100 mg/day per safety concerns. Per investigator discretion, the investigational product was discontinued if safety concerns remained. If the 200 mg/day dose did not control seizures, the dose could have been increased up to 400 mg/day by 50-100 mg/day at greater than or equal to 1 week intervals. A dose greater than 200 mg/day could have been administered in 2 divided doses (in the morning and PM). In the ExP, lamotrigine was administered at 100-400 mg/day based on seizure status/safety. If a dose less than 100 or greater than 400 mg/day was judged to be necessary, the participant was withdrawn from the study.

Serious adverse events	Lamotrigine		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 65 (12.31%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Pulmonary contusion			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sick sinus syndrome			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lamotrigine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 65 (58.46%)		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 65 (21.54%)		
occurrences (all)	26		
Dizziness			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 65 (12.31%)		
occurrences (all)	8		
Drug eruption			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 65 (23.08%) 31		

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