Clinical trial results:
Valproate dose reduction and its clinical evaluation by introducing lamotrigine in Japanese women with epilepsy – single arm, multicenter, and open-label study

Summary

EudraCT number	2017-001515-36
Trial protocol	Outside EU/EEA
Global end of trial date	11 May 2015

Results information

Result version number	v1 (current)
This version publication date	20 October 2017
First version publication date	20 October 2017

Trial information

Trial identification

Sponsor protocol code	200776

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	17 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine whether the VPA dose can be reduced by additional administration of LTG (up to 200 mg/d if there are no safety concerns) in Japanese pre-menopausal female epilepsy patients aged 15 years or older, whose seizures are well controlled by VPA monotherapy (fixed maintenance dose of 400-1200 mg/d).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 April 2014
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: 33
Worldwide total number of subjects	33
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)	6
Adults (18-64 years)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants (par.) receiving monotherapy treatment with sodium valproate (VPA) maintenance dose of 400-1200 milligrams/day [mg/d]) due to a history of partial seizures (including secondary generalized seizures) or tonic-clonic seizures, and whose seizures had been controlled for 12 weeks (wk) prior to start of treatment were enrolled in the study.

Pre-assignment

Screening details:

A total of 33 participants were enrolled into the study and 20 participants completed the study.

Period 1

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

Arms

Arm title	Escalation Phase: LTG plus VPA

Arm description:

Participants received a fixed maintenance dose of VPA (400-1200 mg/d) along with lamotrigine (LTG) which was gradually escalated to 200 mg/d in accordance with the information of package insert: i.e. 25 mg of LTG was orally administered once every other day for the first 2 weeks and then once daily for the following 2 weeks. Thereafter, LTG was gradually escalated by 25 to 50 mg every 1 to 2 weeks for once or twice daily administration. If there were safety concerns, the LTG dose was decreased to 100 mg/d at the discretion of the investigator or sub-investigator. If there were still safety concerns despite the dose reduction to 100 mg/d, LTG was discontinued. The total duration of this phase was 8 to18 weeks.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine 25 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg of Lamotrigine tablet was orally administered once every other day for the first two weeks and then once daily for the next 2 weeks.

Investigational medicinal product name	Lamotrigine 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg of Lamotrigine tablet was orally administered in dose escalation phase once or twice daily depending on the dose escalation.

Investigational medicinal product name	Sodium Valproate 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg extended release tablets were administered as per the dosage instruction on package insert by oral route

Investigational medicinal product name	Sodium Valproate extended release 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 400 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 400 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Number of subjects in period 1	Escalation Phase: LTG plus VPA
Started	33
Completed	20
Not completed	13
Consent withdrawn by subject	3
Adverse event, non-fatal	9
Protocol-defined Stopping Criteria	1

Period 2

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

Arms

Arm title	Reduction Phase: LTG plus VPA

Arm description:

Participants received a range of VPA dose reduction as follows: When VPA was reduced to 300 mg/d, the range of reduction was determined at the discretion of the investigator or sub-investigator: e.g., 1000 mg/d (2 weeks), 800 mg/d (2 weeks), 600 mg/d (2 weeks), 400 mg/d (2 weeks), 300 mg/d OR 1000 mg/d (4 weeks), 600 mg/d (4 weeks), 300 mg/d and when VPA was reduced to less than 300 mg/d, the dose was reduced to 300, 200, 100, and 0 mg/d in 100 mg decrements in steps of at least one week duration. When VPA was concomitantly used, LTG was administered twice daily with 200 mg/d as a maintenance dose. If there were safety concerns during the LTG Escalation Phase, a fixed maintenance dose of 100 to 200 mg/d of LTG was administered twice daily. When VPA was withdrawn (that is, VPA was reduced to 0 mg/d), LTG was required to be increased by 50-100 mg/d. If there were any safety concern, 25 mg increment was also available. The total duration of this phase was 4 to16 weeks.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine 25 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg of Lamotrigine tablet was orally administered once every other day for the first two weeks and then once daily for the next 2 weeks.

Investigational medicinal product name	Lamotrigine 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg of Lamotrigine tablet was orally administered in dose escalation phase once or twice daily depending on the dose escalation.

Investigational medicinal product name	Sodium Valproate 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 100 mg tablets
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg extended release tablets were administered as per the dosage instruction on package insert by oral route

Investigational medicinal product name	Sodium Valproate extended release 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 400 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 400 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Number of subjects in period 2	Reduction Phase: LTG plus VPA
Started	20
Completed	20

Period 3

Period 3 title	LTG and VPA Maintenance Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Maintenance Phase: LTG plus VPA

Arm description:

Participants received two different treatments. In one group, participants received a fixed maintenance dose of LTG 200 mg/d (or 100 to 200 mg/d if there were safety concerns during the LTG Escalation Phase) and VPA 100 mg/d (or higher if seizures occurred during the VPA Reduction Phase) were administered twice and 1-3 times daily, respectively, for 12 weeks. The frequency of administration was not changed. If seizures occurred, VPA dose could be increased/re-introduced. On the other group, after VPA was withdrawn, LTG dose was escalated up to 300 mg/d with 50-100 mg increment per 1-2 weeks. If there was safety concern or if remaining dose to 300 mg/d was below 50 mg, 25 mg increment was also available. If seizures occurred, LTG dose was increased up to 400 mg/d. If there was safety concern, LTG dose was decreased to 100 mg/d. If there was still safety concern at 100 mg/d, the participants were discontinued from the study. The total duration of this phase was 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine 25 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg of Lamotrigine tablet was orally administered once every other day for the first two weeks and then once daily for the next 2 weeks.

Investigational medicinal product name	Lamotrigine 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg of Lamotrigine tablet was orally administered in dose escalation phase once or twice daily depending on the dose escalation.

Investigational medicinal product name	Sodium Valproate 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 100 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 100 mg extended release tablets were administered as per the dosage instruction on package insert by oral route

Investigational medicinal product name	Sodium Valproate extended release 200 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 200 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Investigational medicinal product name	Sodium Valproate extended release 400 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sodium Valproate 400 mg extended release tablets were administered as per the dosage instruction on package insert by oral route.

Number of subjects in period 3	Maintenance Phase: LTG plus VPA
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	LTG Escalation Phase
Reporting group description: LTG Escalation Phase	

Reporting group values	LTG Escalation Phase	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years arithmetic mean standard deviation	 25.6 ± 7.73	 -	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	33	33	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
Asian- Japanese Heritage	33	33	

End points

End points reporting groups

Reporting group title	Escalation Phase: LTG plus VPA

Reporting group description:

Participants received a fixed maintenance dose of VPA (400-1200 mg/d) along with lamotrigine (LTG) which was gradually escalated to 200 mg/d in accordance with the information of package insert: i.e. 25 mg of LTG was orally administered once every other day for the first 2 weeks and then once daily for the following 2 weeks. Thereafter, LTG was gradually escalated by 25 to 50 mg every 1 to 2 weeks for once or twice daily administration. If there were safety concerns, the LTG dose was decreased to 100 mg/d at the discretion of the investigator or sub-investigator. If there were still safety concerns despite the dose reduction to 100 mg/d, LTG was discontinued. The total duration of this phase was 8 to18 weeks.

Reporting group title	Reduction Phase: LTG plus VPA

Reporting group description:

Participants received a range of VPA dose reduction as follows: When VPA was reduced to 300 mg/d, the range of reduction was determined at the discretion of the investigator or sub-investigator: e.g., 1000 mg/d (2 weeks), 800 mg/d (2 weeks), 600 mg/d (2 weeks), 400 mg/d (2 weeks), 300 mg/d OR 1000 mg/d (4 weeks), 600 mg/d (4 weeks), 300 mg/d and when VPA was reduced to less than 300 mg/d, the dose was reduced to 300, 200, 100, and 0 mg/d in 100 mg decrements in steps of at least one week duration. When VPA was concomitantly used, LTG was administered twice daily with 200 mg/d as a maintenance dose. If there were safety concerns during the LTG Escalation Phase, a fixed maintenance dose of 100 to 200 mg/d of LTG was administered twice daily. When VPA was withdrawn (that is, VPA was reduced to 0 mg/d), LTG was required to be increased by 50-100 mg/d. If there were any safety concern, 25 mg increment was also available. The total duration of this phase was 4 to16 weeks.

Reporting group title	Maintenance Phase: LTG plus VPA

Reporting group description:

Participants received two different treatments. In one group, participants received a fixed maintenance dose of LTG 200 mg/d (or 100 to 200 mg/d if there were safety concerns during the LTG Escalation Phase) and VPA 100 mg/d (or higher if seizures occurred during the VPA Reduction Phase) were administered twice and 1-3 times daily, respectively, for 12 weeks. The frequency of administration was not changed. If seizures occurred, VPA dose could be increased/re-introduced. On the other group, after VPA was withdrawn, LTG dose was escalated up to 300 mg/d with 50-100 mg increment per 1-2 weeks. If there was safety concern or if remaining dose to 300 mg/d was below 50 mg, 25 mg increment was also available. If seizures occurred, LTG dose was increased up to 400 mg/d. If there was safety concern, LTG dose was decreased to 100 mg/d. If there was still safety concern at 100 mg/d, the participants were discontinued from the study. The total duration of this phase was 12 weeks.

Subject analysis set title	LTG plus VPA (Phase 1, 2 and 3)
Subject analysis set type	Full analysis

Subject analysis set description:

Par. received a fixed maintenance (maint) dose of VPA (400-1200 mg/d) along with LTG gradually escalated to 200 mg/d in accordance with the package insert information: i.e. 25 mg of LTG was orally administered once every other day for the first 2 wk and then once daily for the following 2 wk. Thereafter, LTG was gradually escalated by 25 to 50 mg every 1 to 2 wk for once or twice daily administration. Par. received a range of VPA dose reduction as follows: When VPA was reduced to 300 mg/d, the range of reduction was as follows: 1000 mg/d (2 wk), 800 mg/d (2 wk), 600 mg/d (2 wk), 400 mg/d (2 wk), 300 mg/d OR 1000 mg/d (4 wk), 600 mg/d (4 wk), 300 mg/d and when VPA was reduced to < 300 mg/d, the dose was reduced to 300, 200, 100 and 0 mg/d in 100 mg decrements in steps of at least one wk duration. Par. received a fixed maint dose of LTG 200 mg/d and VPA 100 mg/d or a maint dose of LTG 200-400 mg/d were administered twice and 1-3 times daily for LTG and VPA, respectively, for 12 wk.

Primary: Percentage of participants who achieved reduction in daily VPA dose

End point title	Percentage of participants who achieved reduction in daily VPA dose[1]

End point description:

The VPA dose reduction from Baseline is defined as post VPA dose minus the Baseline VPA dose < 0. Baseline VPA dose is the dose at the Baseline visit (Week 0) and the post VPA dose is the last VPA dose during the LTG and VPA Maintenance Phase. Percentage of participants with dose reduction during the LTG and VPA Maintenance Phase is presented. Full analysis set (FAS): comprised of all participants in the Safety Population who provided at least one efficacy data after the first dose of the investigational product during the LTG Escalation Phase.

End point type	Primary

End point timeframe:

Baseline and at the end of the LTG and VPA Maintenance Phase, 24-46 weeks that can be varied by durations of the LTG Escalation Phase and VPA Reduction Phase

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	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[2]			
Units: Percentage of participants				
number (confidence interval 95%)	60.6 (42.14 to 77.09)			

Notes:

[2] - FAs population

Statistical analyses

No statistical analyses for this end point

Primary: Percent change in the VPA dose

End point title	Percent change in the VPA dose[3]

End point description:

Percent change in VPA dose is calculated as (pre-dose - post-dose) / pre-dose x 100. Pre-dose is the VPA dose at the Baseline visit and post-dose is the last VPA dose during the LTG and VPA Maintenance Phase.

End point type	Primary

End point timeframe:

Baseline and at the end of the LTG and VPA Maintenance Phase, 24-46 weeks that can be varied by durations of the LTG Escalation Phase and VPA Reduction Phase

Notes:

[3] - 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	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[4]			
Units: Percentage of reduction				
arithmetic mean (standard deviation)	-60.10 (± 49.290)			

Notes:

[4] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days in total that epileptic seizures occurred up to the LTG and VPA Maintenance Phase

End point title	Number of days in total that epileptic seizures occurred up to the LTG and VPA Maintenance Phase

End point description:

The participants with no seizure, had no record in seizure dairy. Only those participants with more than one seizure were assessed for this Outcome Measure.

End point type	Secondary

End point timeframe:

Baseline and up to 46 weeks

End point values	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[5]			
Units: Days	2			

Notes:

[5] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in quality of life in epilepsy-31-P (QOLIE-31-P) in participants aged 18 years and older

End point title	Change from Baseline in quality of life in epilepsy-31-P (QOLIE-31-P) in participants aged 18 years and older

End point description:

QOLIE-31-P is a questionnaire analyzed according to the scoring manual at Baseline, at the end of LTG/VPA Maintenance Phase and withdrawals for the participants aged 18 years and older (n=26, excluding 1 participant withdrawn due to protocol violation). Overall score was calculated as an average of sub scores that were normalized to 0 to 100. QOLIE-31-P has 7 subscale items (energy, mood, daily activities, cognition, medication effect, seizure worry and overall QOL). Higher score presents higher quality of life. Epileptic symptoms generally affect the QOL of participants, and so QOLIE-31-P is world widely used for the QOL assessment of adult participants. Baseline is defined as Day 1 (pre-dose) value. Change from Baseline is calculated as post-dose visit value minus Baseline value. Only those participants available at the indicated phase were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to 46 weeks

End point values	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[6]			
Units: Scores on a scale				
arithmetic mean (standard deviation)				

LTG Escalation-Withdrawal, n=10	-7.19 (± 7.531)			
LTG and VPA Maintenance-Visit 5, n=16	0.19 (± 9.082)			

Notes:

[6] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in quality of life in epilepsy for adolescents (QOLIE-AD-48) in participants aged 15-17 years

End point title	Change from Baseline in quality of life in epilepsy for adolescents (QOLIE-AD-48) in participants aged 15-17 years

End point description:

QOLIE-AD-48 is a questionnaire analyzed according to the scoring manual at Baseline, at the end of the LTG/VPA Maintenance Phase and withdrawals for participants aged 15-17 years (n=6). Particpants who has started by QOLIE-AD-48 were using the same questionnaire even after 18 years old. Overall score was calculated as an average of sub scores that were normalized to 0 to 100. QOLIE-AD-48 has 8 subscale items (epilepsy impact, memory/concentration, physical fuctioning, stigma, social support, school behavior, attitudes towards epilepsy and health perceptions). Higher score presents higher quality of life. Epileptic symptoms generally affect the QOL of participants, and so QOLIE-AD-48 is world widely used for the QOL assessment of non-adult participants. Baseline is defined as Day 1 (pre-dose) value. Change from Baseline is calculated as post-dose visit value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline and up to 46 weeks

End point values	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[7]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
LTG Escalation-Withdrawal, n=2	-10.83 (± 11.862)			
LTG and VPA Maintenance-Visit 5, n=4	-2.67 (± 6.356)			

Notes:

[7] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who completed or discontinued from the study

End point title	Percentage of participants who completed or discontinued from the study

End point description:

Following cases were considered for participants to have completed a part of or whole of the study. For

whole period completion: participants who completed the last LTG and VPA Maintenance Phase visit (M5) in the LTG and VPA Maintenance Phase and follow-up examination. For LTG Escalation Phase completion: participants who reached 200 mg/d of LTG (or 100-200 mg/d of LTG if there were safety concerns) within 8-18 weeks of the phase. For VPA Reduction Phase completion: participants who completed the last fixed dose of VPA Reduction Phase visit (0 mg/d) (FR4) of the phase. For LTG and VPA Maintenance Phase completion: participants who completed M5 of the phase. Participants who met any of the withdrawal criteria after the start of investigational product were considered to have discontinued the study. Percentage of participants who completed or discontinued/withdrawn from the study is presented. Enrolled Population: comprised of all participants who had a Baseline (Week 0) visit.

End point type	Secondary

End point timeframe:

Up to 50 weeks

End point values	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[8]			
Units: Percentage of participants				
Completed	61			
Withdrawn	39			

Notes:

[8] - Enrolled Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs), AEs leading to discontinuation of the investigational product and/or withdrawal from the study, drug-related AEs, deaths and serious adverse events (SAEs) throughout the study

End point title	Number of participants with adverse events (AEs), AEs leading to discontinuation of the investigational product and/or withdrawal from the study, drug-related AEs, deaths and serious adverse events (SAEs) throughout the study

End point description:

An AE is defined as untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, is a congenital anomaly/birth defect, based on medical or scientific judgement and all events of possible drug-induced liver injury. Safety Population: comprised of participants who received at least one dose of the investigational product during the LTG Escalation Phase.

End point type	Secondary

End point timeframe:

From the start of study treatment until follow-up (up to 50 weeks)

End point values	LTG plus VPA (Phase 1, 2 and 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	33[9]			
Units: Participants				
Any AEs	30			
Drug-related AEs	17			
Any SAEs	4			
AEs leading to discontinuation/withdrawal	9			
AEs leading to death	0			

Notes:

[9] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious adverse events (SAEs) were collected from the start of study treatment and until the follow-up contact (up to 50 weeks).

Adverse event reporting additional description:

AEs and SAEs were collected from participants of the safety population, comprised of all participants who received atleast one dose of the investigational product during the LTG Escalation Phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	LTG plus VPA (Phase 1, 2 and 3)

Reporting group description:

Par. received a fixed maintenance (maint) dose of VPA (400-1200 mg/d) along with LTG gradually escalated to 200 mg/d in accordance with the package insert information: i.e. 25 mg of LTG was orally administered once every other day for the first 2 wk and then once daily for the following 2 wk. Thereafter, LTG was gradually escalated by 25 to 50 mg every 1 to 2 wk for once or twice daily administration. Par. received a range of VPA dose reduction as follows: When VPA was reduced to 300 mg/d, the range of reduction was as follows: 1000 mg/d (2 wk), 800 mg/d (2 wk), 600 mg/d (2 wk), 400 mg/d (2 wk), 300 mg/d OR 1000 mg/d (4 wk), 600 mg/d (4 wk), 300 mg/d and when VPA was reduced to < 300 mg/d, the dose was reduced to 300, 200, 100 and 0 mg/d in 100 mg decrements in steps of at least one wk duration. Par. received a fixed maint dose of LTG 200 mg/d and VPA 100 mg/d or a maint dose of LTG 200-400 mg/d were administered twice and 1-3 times daily for LTG and VPA, respectively, for 12 wk.

Serious adverse events	LTG plus VPA (Phase 1, 2 and 3)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytic necrotising lymphadenitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LTG plus VPA (Phase 1, 2 and 3)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 33 (69.70%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nervous system disorders			
Somnolence			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Dizziness			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Drug eruption			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 33 (6.06%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 9 / 33 (27.27%) 13 4 / 33 (12.12%) 5 3 / 33 (9.09%) 3		

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