



Clinical trial results: Lamotrigine And Borderline Personality Disorder: Investigating Long-Term Effectiveness

Summary

EudraCT number	2012-003136-23
Trial protocol	GB
Global end of trial date	22 September 2016

Results information

Result version number	v1 (current)
This version publication date	07 September 2017
First version publication date	07 September 2017

Trial information

Trial identification

Sponsor protocol code	CRO1990
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Additional study identifiers

ISRCTN number	ISRCTN90916365
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Faculty of Medicine, London, United Kingdom, SW7 2AZ
Public contact	Clinical Trials Office, Imperial College London, 44 2073861220, v.leeson@imperial.ac.uk
Scientific contact	Clinical Trials Office, Imperial College London, 44 2073861220, v.leeson@imperial.ac.uk

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2016
Global end of trial reached?	Yes
Global end of trial date	22 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study are as follows:

- i. To test whether adding lamotrigine to usual care for adults with borderline personality disorder (BPD) improves mental health over a 52 week period, in comparison to a placebo control.
- ii. To examine whether the addition of lamotrigine to usual care for adults with BPD improves social functioning and quality of life, reduces the incidence of suicidal behaviour, and lowers the amount of antipsychotic and other psychotropic medication that people are prescribed, in comparison to a placebo control.
- iii. To compare the incidence of side effects among those prescribed lamotrigine in addition to usual care for adults with BPD, in comparison to a placebo control.
- iv. To examine the cost, cost-utility and cost-effectiveness of adding lamotrigine to usual care for adults with BPD, in comparison to a placebo control.

Protection of trial subjects:

Thorough monitoring of adverse events and participant wellbeing occurred as part of the assessment process. During assessment and testing breaks were provided to minimise possible fatigue or stress, and if indicated, the assessment were spread over more than one visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 276
Worldwide total number of subjects	276
EEA total number of subjects	276

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	276
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Age 18+.
- Fulfills DSM-IV diagnostic criteria for BPD.
- Does not fulfil criteria for Bipolar affective disorder (type I & II), or psychotic disorder
- Receiving a mood stabiliser
- Medical history of liver or kidney impairment.
- Cognitive or language difficulties.
- Pregnant, planning a pregnancy or not using adequate contraception.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	lamotrigine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	lamotrigine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For those not taking a combined hormonal contraceptive, the starting dose will be 25mg per day. Depending on the response and tolerance it will be increased to 50mg after two weeks, 100mg after four weeks and 200mg thereafter. If there are problems with tolerability at 200mg, the clinician can reduce the dose back to 100mg/day. For those who are taking a combined hormonal contraceptive the starting dose will be 25mg per day. This will be increased to 50mg after two weeks, 100mg after four weeks, 200mg after six weeks, 300mg after eight weeks, and 400mg after ten weeks (see example (b) below). If there are problems with tolerability at 400mg, the clinician can reduce the dose back to 200 or 100 mg/day. Where a participant misses five or more consecutive days of the medication at any time during their participation dose titration will be restarted.

Arm title	placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administration was matched to the active (lamotrigine) arm.

Number of subjects in period 1	lamotrigine	placebo
Started	137	139
Completed	97	98
Not completed	40	41
Adverse event, serious fatal	-	3
Consent withdrawn by subject	14	12
Adverse event, non-fatal	4	1
Other	6	5
Lost to follow-up	16	20

Baseline characteristics

Reporting groups

Reporting group title	lamotrigine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	lamotrigine	placebo	Total
Number of subjects	137	139	276
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	36	36.2	
standard deviation	± 11	± 11	-
Gender categorical Units: Subjects			
Female	103	105	208
Male	34	34	68

End points

End points reporting groups

Reporting group title	lamotrigine
Reporting group description:	-
Reporting group title	placebo
Reporting group description:	-

Primary: ZAN-BPD

End point title	ZAN-BPD
End point description:	
End point type	Primary
End point timeframe:	
52 week assessment	

End point values	lamotrigine	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: rating				
arithmetic mean (standard deviation)	11.3 (± 6.6)	11.5 (± 7.7)		

Statistical analyses

Statistical analysis title	ZAN-BPD score at 52 weeks
Statistical analysis description:	
For primary analysis of ZAN-BPD score at 52 weeks follow up, randomised groups will be compared using a generalised linear model for continuous outcome adjusted by baseline ZAN-BPD score, centre, severity of personality disorder (simple or complex) and the extent of bipolarity (score ≥ 14 or < 14). The effectiveness parameter comparing lamotrigine plus usual care with usual care alone will be the difference in mean ZAN-BPD score at 52 weeks along with 95% confidence interval and exact p value.	
Comparison groups	lamotrigine v placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.906
Method	generalised linear model
Parameter estimate	adjusted difference in mean
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

8 July 2013 to 22 Sept 2016

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	lamotrigine
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	lamotrigine	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 137 (18.98%)	32 / 139 (23.02%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Induced abortion			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	2 / 137 (1.46%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cyst			

subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 137 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Social circumstances			
Recreational drug use			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitated			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deliberate self-harm			
subjects affected / exposed	4 / 137 (2.92%)	4 / 139 (2.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional distress			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intentional overdose			
subjects affected / exposed	11 / 137 (8.03%)	6 / 139 (4.32%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental distress			
subjects affected / exposed	2 / 137 (1.46%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic episode			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	5 / 137 (3.65%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	3 / 137 (2.19%)	5 / 139 (3.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal intention			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 137 (0.73%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoughts of self-harm			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Violent ideation			

subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional drug misuse			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	3 / 137 (2.19%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohns disease aggravated			
subjects affected / exposed	2 / 137 (1.46%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney function abnormal			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
painful arm			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess on buttock			
subjects affected / exposed	1 / 137 (0.73%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic reaction			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 137 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	lamotrigine	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 137 (56.20%)	93 / 139 (66.91%)	
Injury, poisoning and procedural complications			

Bruising subjects affected / exposed occurrences (all)	10 / 137 (7.30%) 13	0 / 139 (0.00%) 0	
Intentional overdose subjects affected / exposed occurrences (all)	14 / 137 (10.22%) 15	9 / 139 (6.47%) 11	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 5	9 / 139 (6.47%) 9	
Headache subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 8	5 / 139 (3.60%) 5	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	15 / 137 (10.95%) 19	10 / 139 (7.19%) 11	
Nausea subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 10	6 / 139 (4.32%) 6	
Vomiting subjects affected / exposed occurrences (all)	9 / 137 (6.57%) 10	7 / 139 (5.04%) 7	
Skin and subcutaneous tissue disorders			
Skin rash subjects affected / exposed occurrences (all)	11 / 137 (8.03%) 13	11 / 139 (7.91%) 11	
Psychiatric disorders			
Deliberate Self-Harm subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 8	7 / 139 (5.04%) 8	
Suicidal ideation subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 7	8 / 139 (5.76%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2013	<ol style="list-style-type: none"><li data-bbox="419 360 1426 421">1. The addition of the International Personality Disorder Examination (IPDE) at screening.<li data-bbox="419 450 1426 510">2. The addition of the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) assessment at the 52 week follow-up assessment.<li data-bbox="419 539 1426 600">3. The wording in the protocol of "combined oral contraceptive pill" has been replaced by "combined hormonal contraceptive"<li data-bbox="419 629 1426 689">4. Additional information pertaining to trial medication supply added to the protocol.<li data-bbox="419 719 1426 779">5. Additional information pertaining to dispensing and accountability added to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported