Clinical trial results:
Interventional, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of brexpiprazole (1 and 3 mg/day) as adjunctive treatment in elderly patients with major depressive disorder with an inadequate response to antidepressant treatment

THE STUDY WAS PREMATURELY TERMINATED AND NO FIRM CONCLUSIONS CAN BE DRAWN REGARDING SAFETY AND EFFICACY

Summary

EudraCT number	2012-001361-32
Trial protocol	SE LT FI SK EE BG GB PL RO
Global end of trial date	22 May 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	14571A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01837797
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9,, Valby, Denmark,
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 45 36301 311, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 45 36301 311, LundbeckClinicalTrials@lundbeck.com

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	22 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2014
Global end of trial reached?	Yes
Global end of trial date	22 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Efficacy on depressive symptoms of brexpiprazole versus placebo as adjunctive treatment to antidepressants in elderly patients with an inadequate response to antidepressant treatment

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996)

Background therapy:

standard antidepressant treatment, specifically; escitalopram, fluoxetine, sertraline, paroxetine IR, venlafaxine XR, duloxetine

Evidence for comparator: -

Actual start date of recruitment	15 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Lithuania: 3
Country: Number of subjects enrolled	United States: 67
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	Russian Federation: 10
Worldwide total number of subjects	129
EEA total number of subjects	48

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)	0
Adults (18-64 years)	0
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the investigator's own patient population, via advertisement (if allowed in the country), via general pratitioners or or referrals

Pre-assignment

Screening details:

The study consisted of a screening period (could last from 3 to 28 days)

Period 1

Period 1 title	Periode 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	antidepressants treatment with double-blind study treatment

Arm description:

The patients received open-label treatment with one of six commercially available antidepressant antidepressant treatments (ADT) together with double-blind study treatment

Arm type	Non-investigational Medicinal Products
Investigational medicinal product name	Duloxetine (Cymbalta)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg/day, capsules, orally

Investigational medicinal product name	Escitalopram (Cipralex or Lexapro)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 or 10 mg/day, tablets, orally

Investigational medicinal product name	Fluoxetine (Prozac)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 or 40 mg/day, capsules, orally

Investigational medicinal product name	Paroxetine (Paxil or Seroxat)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20, 30 or 40mg/day, orally, tablets

Investigational medicinal product name	Sertraline (Lustral or Zoloft)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
50, 100 or 150 mg/day

Investigational medicinal product name	Venlafaxine (Effexor XL or Effexor XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
75, 150 or 225 mg/day, capsules, orally

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
once daily, tablets, orally for 8 or 10 weeks

Number of subjects in period 1	antidepressants treatment with double-blind study treatment
Started	129
Completed	27
Not completed	102
Consent withdrawn by subject	6
Withdrew consent before ADT	1
Adverse event, non-fatal	9
Administrative or other	76
Other	10

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Brexpiprazole 1 mg and ADT
Arm description:	
Brexpiprazole adjunct to continued open-label treatment with a commercially available ADT received in Period 1	
Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	Lu AF41156
Other name	OPC-34712
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 mg once daily, tablets, orally	

Arm title	Brexpiprazole 3 mg and ADT
Arm description:	
Brexpiprazole adjunct to continued open-label treatment with a commercially available ADT received in Period 1	
Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	Lu AF41156
Other name	OPC-34712
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
3 mg once daily, tablets, orally	

Arm title	Placebo and ADT
Arm description:	
Placebo adjunct to continued open-label treatment with a commercially available ADT	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
once daily, tablets, orally	

Number of subjects in period 2[1]	Brexpiprazole 1 mg and ADT	Brexpiprazole 3 mg and ADT	Placebo and ADT
Started	3	6	6
Completed	1	1	1
Not completed	2	5	5
Adverse event, non-fatal	-	1	-
The study was prematurely terminated	2	4	5

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: Only patients with prospectively assessed inadequate response were randomised to Period 2

Baseline characteristics

Reporting groups	
Reporting group title	Periode 1

Reporting group description: -

Reporting group values	Periode 1	Total	
Number of subjects	129	129	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	129	129	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	70		
standard deviation	± 4.75	-	
Gender categorical Units: Subjects			
Female	99	99	
Male	30	30	

End points

End points reporting groups

Reporting group title	antidepressants treatment with double-blind study treatment
Reporting group description:	
The patients received open-label treatment with one of six commercially available antidepressant antidepressant treatments (ADT) together with double-blind study treatment	
Reporting group title	Brexpiprazole 1 mg and ADT
Reporting group description:	
Brexpiprazole adjunct to continued open-label treatment with a commercially available ADT received in Period 1	
Reporting group title	Brexpiprazole 3 mg and ADT
Reporting group description:	
Brexpiprazole adjunct to continued open-label treatment with a commercially available ADT received in Period 1	
Reporting group title	Placebo and ADT
Reporting group description:	
Placebo adjunct to continued open-label treatment with a commercially available ADT	

Primary: Number of treatment-emergent adverse events

End point title	Number of treatment-emergent adverse events[1]
End point description:	
The primary endpoint was efficacy, however the study was prematurely terminated and the limited number of enrolled patients resulted in insufficient data for meaningful analyses. Therefore treatment-emergent adverse events are disclosed	
End point type	Primary
End point timeframe:	
First dose to follow-up (prematurely terminated)	

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: No comparison between parameters were performed

End point values	Brexpiprazole 1 mg and ADT	Brexpiprazole 3 mg and ADT	Placebo and ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	6	6	
Units: Number	5	2	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First dose to follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Placebo + ADT
Reporting group description: Placebo + ADT	
Reporting group title	Brex 3 mg + ADT
Reporting group description: Brex 3 mg + ADT	
Reporting group title	Brex 1 mg + ADT
Reporting group description: Brex 1 mg + ADT	

Serious adverse events	Placebo + ADT	Brex 3 mg + ADT	Brex 1 mg + ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo + ADT	Brex 3 mg + ADT	Brex 1 mg + ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	2 / 3 (66.67%)
Investigations			
Weight increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Accidental overdose			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Parkinson's disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Gait disturbance			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Bruxism			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	The main reason for the amendment was to correct errors and clarify the current protocol text in various sections of the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2014	The study was prematurely terminated because of recruitment challenges	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination leading to a small number analysed; only AEs reported

Notes: