Clinical trial results:
Interventional, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study of brexpiprazole as adjunctive treatment to paroxetine or sertraline in adult patients suffering from post-traumatic stress disorder (PTSD)

Summary

EudraCT number	2012-004982-41
Trial protocol	EE IT FI SE PL
Global end of trial date	30 October 2015

Results information

Result version number	v1 (current)
This version publication date	12 November 2016
First version publication date	12 November 2016

Trial information

Trial identification

Sponsor protocol code	14865A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987960
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2200
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 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	30 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2015
Global end of trial reached?	Yes
Global end of trial date	30 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of brexpiprazole up to 1-3 mg/day as adjunctive treatment to paroxetine or sertraline on PTSD symptoms

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2013
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	Poland: 51
Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	Finland: 41
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 186
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Serbia: 25
Country: Number of subjects enrolled	Argentina: 14
Worldwide total number of subjects	417
EEA total number of subjects	146

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)	415
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study

Period 1

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

Arms

Arm title	Placebo and PAR/SER

Arm description:

Placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (Paroxetine/Sertraline (PAR/SER))

Arm type	Experimental
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

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

Dosage and administration details:

50 or 100mg/day; tablets, orally;

The dose of sertraline was increased from 50mg/day to 150mg/day during the first 2 weeks. Further dose increase to 200mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 100, 150, or 200mg/day until the Week 8 Visit in steps of 50mg/day per week

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

Dosage and administration details:

20 or 30mg/day; tablets, orally;

From 20mg/day to 30mg/day during the first week. Further dose increase to 40mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 20 or 30 mg/day until the Week 8 Visit in steps of 10mg/day per week.

Number of subjects in period 1	Placebo and PAR/SER
Started	417
Completed	231
Not completed	186
non-compliance with IMP	6
Consent withdrawn by subject	21
Withdrawal of consent before treatmnet	4
Adverse event, non-fatal	24
aministrative or other reason	75
Lost to follow-up	40
Lack of efficacy	4
Protocol deviation	12

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	Placebo and PAR/SER

Arm description:

Randomized placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (PAR/SER)

Arm type	Experimental
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

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

Dosage and administration details:

50 or 100mg/day; tablets, orally;

The dose of sertraline was increased from 50mg/day to 150mg/day during the first 2 weeks. Further dose increase to 200mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 100, 150, or 200mg/day until the Week 8 Visit in steps of 50mg/day per week

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

Dosage and administration details:

20 or 30mg/day; tablets, orally;

From 20mg/day to 30mg/day during the first week. Further dose increase to 40mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 20 or 30 mg/day until the Week 8 Visit in steps of 10mg/day per week.

Arm title	Brexpiprazole and PAR/SER

Arm description:

Randomized brexpiprazole adjunct to open-label treatment with a commercially available approved treatment for PTSD (PAR/SER)

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	Rexulti
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1mg/day for one week, followed by 2mg/day for 3 weeks. Thereafter the dose was flexible and could be adjusted from 1 to 3 mg/day.

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

Dosage and administration details:

20 or 30mg/day; tablets, orally;

From 20mg/day to 30mg/day during the first week. Further dose increase to 40mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 20 or 30 mg/day until the Week 8 Visit in steps of 10mg/day per week.

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

Dosage and administration details:

50 or 100mg/day; tablets, orally;

The dose of sertraline was increased from 50mg/day to 150mg/day during the first 2 weeks. Further dose increase to 200mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 100, 150, or 200mg/day until the Week 8 Visit in steps of 50mg/day per week

Arm title	Placebo and PAR/SER

Arm description:

Continuation of treatment with placebo adjunct to open-label treatment with a commercially available

approved treatment for PTSD (PAR/SER) from Period 1

Arm type	Experimental
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

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

Dosage and administration details:

20 or 30mg/day; tablets, orally;

From 20mg/day to 30mg/day during the first week. Further dose increase to 40mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 20 or 30 mg/day until the Week 8 Visit in steps of 10mg/day per week.

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

Dosage and administration details:

50 or 100mg/day; tablets, orally;

The dose of sertraline was increased from 50mg/day to 150mg/day during the first 2 weeks. Further dose increase to 200mg/day was allowed until the Week 4 Visit. In case of tolerability issues, the dose could be decreased to 100, 150, or 200mg/day until the Week 8 Visit in steps of 50mg/day per week

Number of subjects in period 2[1]	Placebo and PAR/SER	Brexpiprazole and PAR/SER	Placebo and PAR/SER
Started	17	23	190
Completed	12	14	119
Not completed	5	9	71
non-compliance with IMP	-	-	1
Consent withdrawn by subject	-	1	9
Adverse event, non-fatal	-	1	7
Administrative or other reason	5	7	43
Lost to follow-up	-	-	5
Protocol deviation	-	-	6

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: 1 patient completed period 1, but didn't receive treatment in period 2

Baseline characteristics

Reporting groups

Reporting group title	Placebo and PAR/SER

Reporting group description:

Placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (Paroxetine/Sertraline (PAR/SER))

Reporting group values	Placebo and PAR/SER	Total	
Number of subjects	417	417	
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)	417	417	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.53		
standard deviation	± 11.62	-	
Gender categorical Units: Subjects			
Female	255	255	
Male	162	162	

Subject analysis sets

Subject analysis set title	Period 2: Placebo adjunct to open-label treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Period 2: Placebo adjunct to open-label treatment

Subject analysis set title	Period 2: Brexpiprazole adjunct to open-label treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Period 2: Brexpiprazole adjunct to open-label treatment

Reporting group values	Period 2: Placebo adjunct to open-label treatment	Period 2: Brexpiprazole adjunct to open-label treatment	
Number of subjects	17	23	

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)	17	23	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.9	47.6	
standard deviation	± 11.8	± 10.4	
Gender categorical Units: Subjects			
Female	10	11	
Male	7	12	

End points

End points reporting groups

Reporting group title	Placebo and PAR/SER
Reporting group description:	
Placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (Paroxetine/Sertraline (PAR/SER))	
Reporting group title	Placebo and PAR/SER
Reporting group description:	
Randomized placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (PAR/SER)	
Reporting group title	Brexpiprazole and PAR/SER
Reporting group description:	
Randomized brexpiprazole adjunct to open-label treatment with a commercially available approved treatment for PTSD (PAR/SER)	
Reporting group title	Placebo and PAR/SER
Reporting group description:	
Continuation of treatment with placebo adjunct to open-label treatment with a commercially available approved treatment for PTSD (PAR/SER) from Period 1	
Subject analysis set title	Period 2: Placebo adjunct to open-label treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
Period 2: Placebo adjunct to open-label treatment	
Subject analysis set title	Period 2: Brexpiprazole adjunct to open-label treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
Period 2: Brexpiprazole adjunct to open-label treatment	

Primary: Change From Randomisation in PTSD Symptoms Using CAPS-2 Total Score

End point title	Change From Randomisation in PTSD Symptoms Using CAPS-2 Total Score[1]
End point description:	
Clinician-Administered PTSD Scale Part 2 (CAPS-2): 17 items in criteria B, C and D (Corresponding to CAPS-2) will be administered to provide a total score. They are rated on a 5 point scale for frequency from 0 (never or none) to 4 (daily or almost every day), and intensity from 0 (none) to 4 (extreme). The sum of the 17 items gives a toal score ranging from 0 to 136, with a higher score indicating greater symptom severity	
End point type	Primary
End point timeframe:	
Baseline and Week 28	

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: Due to the low number of enrolled patients eligible for randomization and the sponsor's early termination of the study, the primary and secondary efficacy endpoints were not evaluated

End point values	Period 2: Placebo adjunct to open-label treatment	Period 2: Brexpiprazole adjunct to open-label treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: score				
number (not applicable)				

Notes:

[2] - Endpoints were not evaluated see "limitation section"

[3] - Endpoints were not evaluated see "limitation section"

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomisation in Global Clinical Impression Using CGI-S Score

End point title	Change From Randomisation in Global Clinical Impression Using CGI-S Score

End point description:

Clinical Global Impression - Severity of Illness (CGI-S)
The CGI-S provides the clinician's impression of the patient's current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (Normal - not at all ill) to 7 (among the most extremely ill patients).

End point type	Secondary

End point timeframe:

Baseline and Week 28

End point values	Period 2: Placebo adjunct to open-label treatment	Period 2: Brexpiprazole adjunct to open-label treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[4]	0[5]		
Units: score				
number (not applicable)				

Notes:

[4] - Endpoints were not evaluated see "limitation section"

[5] - Endpoints were not evaluated see "limitation section"

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomisation in Functioning Using SDS Score

End point title	Change From Randomisation in Functioning Using SDS Score

End point description:

Sheehan Disability Scale (SDS)
The SDS is a series of patient self-rated, 10-point visual analogue scales designed to measure the extent to which the patient's life is impaired by panic, anxiety, phobic or depressive symptoms. There are verbal descriptors for the points on the scales as well as numerical scores that provide more precise levels of the verbal descriptors. The patient rates the extent to which his or her 1) work, 2) social life or leisure activities, and 3) home life or family responsibilities are impaired by his or her symptoms, with a higher score indicating greater symptom severity

End point type	Secondary

End point timeframe:

Baseline and Week 28

End point values	Period 2: Placebo adjunct to open-label treatment	Period 2: Brexpiprazole adjunct to open-label treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[6]	0[7]		
Units: Score				
number (not applicable)				

Notes:

[6] - Endpoints were not evaluated see "limitation section"

[7] - Endpoints were not evaluated see "limitation section"

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 adjunct to open-label treatment
Reporting group description: Placebo + PAR/SER	
Reporting group title	Brexpiprazole adjunct to open-label treatment
Reporting group description: Brex + PAR/SER	

Serious adverse events	Placebo adjunct to open-label treatment	Brexpiprazole adjunct to open-label treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo adjunct to open-label treatment	Brexpiprazole adjunct to open-label treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)	3 / 23 (13.04%)	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 17 (5.88%)	2 / 23 (8.70%)	
occurrences (all)	1	3	
Tendon rupture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Disturbance in attention			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Galactorrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

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? Yes

Date	Interruption	Restart date
27 August 2015	The study was terminated 27th of August 2015 due to challenges with patient eligibility; the decision to terminate was not based on any safety concerns. Last patient last visit was 30th of October 2015 (the date of last protocol-specified contact with any patient)	-

Notes:

Limitations and caveats

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

As the study was terminated limited efficacy and safety data were collected from the randomized patients. As a result no efficacy analyses were performed in accordance with the ICH E3 and thus not reported in the abbreviated clinical study report.

Notes: