Clinical trial results:
Interventional, Randomised, Double-blind, Parallel-group, Placebo-controlled, Flexible-dose Long-term Study to Evaluate the Maintenance of Efficacy and Safety of 1 to 3 mg/Day of Brexpiprazole as Adjunctive Treatment in Patients With Major Depressive Disorder With an Inadequate Response to Antidepressant Treatment (ADT)

Summary

EudraCT number	2012-001380-76
Trial protocol	EE SE FI LT GB BG IT LV PL
Global end of trial date	08 June 2016

Results information

Result version number	v1 (current)
This version publication date	24 June 2017
First version publication date	24 June 2017

Trial information

Trial identification

Sponsor protocol code	14570A ARGO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01838681
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
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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	08 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2016
Global end of trial reached?	Yes
Global end of trial date	08 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the maintenance of efficacy on depressive symptoms during long-term treatment of 1 to 3 mg once daily brexpiprazole versus placebo as adjunctive treatment to antidepressants in patients with an inadequate response to antidepressant treatment (ADT)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 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	Bulgaria: 119
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Estonia: 161
Country: Number of subjects enrolled	Finland: 136
Country: Number of subjects enrolled	Germany: 325
Country: Number of subjects enrolled	Latvia: 84
Country: Number of subjects enrolled	Lithuania: 76
Country: Number of subjects enrolled	Mexico: 72
Country: Number of subjects enrolled	Poland: 325
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 121
Country: Number of subjects enrolled	Sweden: 85
Country: Number of subjects enrolled	Ukraine: 189
Country: Number of subjects enrolled	United Kingdom: 168
Country: Number of subjects enrolled	United States: 78
Worldwide total number of subjects	1986
EEA total number of subjects	1494

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)	1857
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1986 patients were enrolled; 1982 received open-label ADT plus double-blind placebo in the 8-week Period A. In the 24-week Period B, 886 patients were randomised and 885 were treated with open-label ADT plus double-blind brexpiprazole or placebo. Non-randomised patients continued in Period A+ and received open-label ADT plus double-blind placebo.

Period 1

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

Arms

Arm title	Period A, Placebo and ADT (8 weeks)

Arm description:

Placebo adjunct to open label treatment with ATD.

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:

One daily

Number of subjects in period 1	Period A, Placebo and ADT (8 weeks)
Started	1986
Completed	1661
Not completed	325
Early response	148
Consent withdrawn by subject	70
Adverse event, non-fatal	39
Administrative or other reason	17
Withdrawal before treatment	4
Lost to follow-up	4
Non-compliance with IMP	6
Protocol deviation	16
Lack of efficacy	21

Period 2

Period 2 title	Treatment period (Period B/A+)
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	Period B, Placebo and ADT (24 weeks randomised treatment)

Arm description:

Placebo adjunct to open-label treatment with a commercially available antidepressant (ADT)

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

Arm title	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)

Arm description:

Brexpiprazole adjunct to ADT. 1, 2, or 3 mg/day, once daily dose. Uptitration in weekly steps from 1 mg/day

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

Dosage and administration details:

One daily. 1, 2, or 3 mg/day, once daily dose, tablets, orally. Uptitration in weekly steps from 1 mg/day

Arm title	Period A+, Placebo and ADT (Non-randomised Patients)

Arm description:

Placebo adjunct to open label treatment with ATD.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)	Period A+, Placebo and ADT (Non-randomised Patients)
Started	442	444	770
Completed	380	349	653
Not completed	62	95	117
Consent withdrawn by subject	28	35	47
Adverse event, non-fatal	13	27	16
Administrative or other reason	6	10	28
Withdrawal before treatment	1	-	-
Lost to follow-up	2	5	11
Non-compliance with IMP	2	3	3
Lack of efficacy	9	11	6
Protocol deviation	1	4	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: 5 patients completed Period A but never started in Period B/A+

Baseline characteristics

Reporting groups

Reporting group title	Period A

Reporting group description: -

Reporting group values	Period A	Total	
Number of subjects	1986	1986	
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)	1857	1857	
From 65-84 years	129	129	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	47.3		
standard deviation	± 12	-	
Gender categorical Units: Subjects			
Female	1402	1402	
Male	584	584	
Race Units: Subjects			
Asian	3	3	
Black or African American	19	19	
White	1918	1918	
Unknown or Not reported	46	46	

End points

End points reporting groups

Reporting group title	Period A, Placebo and ADT (8 weeks)
Reporting group description:	
Placebo adjunct to open label treatment with ATD.	
Reporting group title	Period B, Placebo and ADT (24 weeks randomised treatment)
Reporting group description:	
Placebo adjunct to open-label treatment with a commercially available antidepressant (ADT)	
Reporting group title	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)
Reporting group description:	
Brexpiprazole adjunct to ADT. 1, 2, or 3 mg/day, once daily dose. Uptitration in weekly steps from 1 mg/day	
Reporting group title	Period A+, Placebo and ADT (Non-randomised Patients)
Reporting group description:	
Placebo adjunct to open label treatment with ATD.	

Primary: Full remission during the randomised treatment period

End point title	Full remission during the randomised treatment period
End point description:	
Full remission is defined as a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment. The MADRS is a depression rating scale consisting of 10 items, each rated 0 to 6. The 10 items represent the core symptoms of depressive illness. The overall score ranges from 0 (symptoms absent) to 60 (severe depression). The MADRS total score is the sum of the 10 items.	
End point type	Primary
End point timeframe:	
From randomisation to end of Period B (24 weeks)	

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Number	110	95		

Statistical analyses

Statistical analysis title	Full remission during the rand. treatment period
Comparison groups	Period B, Placebo and ADT (24 weeks randomised treatment) v Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)

Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2641 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.15

Notes:

[1] - Model included MADRS total score at the randomisation visit, treatment group, country, and the randomisation criteria used

Secondary: Full functional remission during the randomised treatment period

End point title	Full functional remission during the randomised treatment period

End point description:

Full functional remission is defined as a Sheehan Disability Scale (SDS) total score <=6 and all SDS domain scores <=2 observed for at least 8 consecutive weeks during the randomised treatment period. The SDS assesses functional impairment in 3 domains: work/school, social life or leisure activities, and home life or family responsibilities. The participant rates the extent to which each aspect is impaired on a 10-point visual analog scale, from 0 (not at all) to 10 (extremely). The 3 scores are added together to calculate the total score, which ranges from 0 to 30, with higher scores indicating more impairment.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Number	73	68		

Statistical analyses

No statistical analyses for this end point

Secondary: Full global score remission during the randomised treatment period

End point title	Full global score remission during the randomised treatment period

End point description:

Full global score remission is defined as a Clinical Global Impression - Severity of Illness (CGI-S) score <=2 observed for at least 8 consecutive weeks during the randomised treatment period. The CGI-S is a 7-point scale where the clinician rates the severity of the patient's illness at the time of assessment,

relative to the clinician's past experience with patients who have the same diagnosis, on the following scale: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Number	143	121		

Statistical analyses

No statistical analyses for this end point

Secondary: Total time in remission during the randomised treatment period

End point title	Total time in remission during the randomised treatment period

End point description:

The total time the patient spends in remission during randomised treatment. Remission is defined as a MADRS total score <=10 and a >=50% decrease from randomisation in MADRS total score. Time in remission is defined as the sum of days over all periods between Period B visits where remission was obtained. The period between two visits is counted as in remission if the patient was in remission when the period started.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Number of days				
arithmetic mean (standard deviation)	33.5 (± 46.1)	30 (± 44.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to full remission during the randomised treatment period

End point title	Time to full remission during the randomised treatment period

End point description:

The time from randomisation until full remission has been obtained. Full remission is defined as a MADRS total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment. The time to full remission was calculated using Kaplan-Meier Methods.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Days	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Full remission sustained during the randomised treatment period

End point title	Full remission sustained during the randomised treatment period

End point description:

Full remission sustained is defined as having obtained full remission and remain in remission until completion of the study. Full remission is defined as a MADRS total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	444		
Units: Number	105	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 6 in MADRS total score during the randomised treatment period

End point title	Change from randomisation to Week 6 in MADRS total score during the randomised treatment period

End point description:

The MADRS is a depression rating scale consisting of 10 items, each rated 0 to 6. The 10 items represent the core symptoms of depressive illness. The overall score ranges from 0 (symptoms absent) to 60 (severe depression). The MADRS total score is the sum of the 10 items.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 Weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	422		
Units: Units on a scale				
least squares mean (standard error)	-5.9 (± 0.4)	-6.3 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 24 in MADRS total score during the randomised treatment period

End point title	Change from randomisation to Week 24 in MADRS total score during the randomised treatment period

End point description:

The MADRS is a depression rating scale consisting of 10 items, each rated 0 to 6. The 10 items represent the core symptoms of depressive illness. The overall score ranges from 0 (symptoms absent) to 60 (severe depression). The MADRS total score is the sum of the 10 items.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	333		
Units: Units on a scale				
least squares mean (standard error)	-12.6 (± 0.6)	-11.5 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 6 During the Randomised Treatment Period

End point title	Response at Week 6 During the Randomised Treatment Period

End point description:

Response is defined as a >=50% decrease from randomisation in MADRS total score.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	440	442		
Units: Number	76	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 24 during the randomised treatment period

End point title	Response at Week 24 during the randomised treatment period

End point description:

Response is defined as a >=50% decrease from randomisation in MADRS total score.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	440	442		
Units: Number	236	223		

Statistical analyses

No statistical analyses for this end point

Secondary: Remission at Week 6 During the Randomised Treatment Period

End point title	Remission at Week 6 During the Randomised Treatment Period

End point description:

Remission is defined as a MADRS total score <=10 and a >=50% decrease from randomisation in MADRS total score.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	440	442		
Units: Number	46	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Remission at Week 24 in the randomised treatment period

End point title	Remission at Week 24 in the randomised treatment period

End point description:

Remission is defined as a MADRS total score <=10 and a >=50% decrease from randomisation in

MADRS total score.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	440	442		
Units: Number	198	176		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 6 in SDS total score during the randomised treatment period

End point title	Change from randomisation to Week 6 in SDS total score during the randomised treatment period

End point description:

The SDS assesses functional impairment in 3 domains: work/school, social life or leisure activities, and home life or family responsibilities. The participant rates the extent to which each aspect is impaired on a 10-point visual analog scale, from 0 (not at all) to 10 (extremely). The 3 scores are added together to calculate the total score, which ranges from 0 to 30, with higher scores indicating more impairment.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Units on scale				
least squares mean (standard error)	-3 (± 0.3)	-2.9 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 24 in SDS total score during the randomised treatment period

End point title	Change from randomisation to Week 24 in SDS total score during the randomised treatment period

End point description:

The SDS assesses functional impairment in 3 domains: work/school, social life or leisure activities, and home life or family responsibilities. The participant rates the extent to which each aspect is impaired on a 10-point visual analog scale, from 0 (not at all) to 10 (extremely). The 3 scores are added together to calculate the total score, which ranges from 0 to 30, with higher scores indicating more impairment.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	333		
Units: Unit on a scale				
least squares mean (standard error)	-6.7 (± 0.5)	-5.5 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 6 in CGI-S score during the randomised treatment period

End point title	Change from randomisation to Week 6 in CGI-S score during the randomised treatment period

End point description:

The CGI-S is a 7-point scale where the clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis on the following scale: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	422		
Units: Units on a scale				
least squares mean (standard error)	-0.8 (± 0.1)	-0.8 (± 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 24 in CGI-S score during the randomised treatment period

End point title	Change from randomisation to Week 24 in CGI-S score during the randomised treatment period

End point description:

The CGI-S is a 7-point scale where the clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis on the following scale: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	333		
Units: Unit on a scale				
least squares mean (standard error)	-1.7 (± 0.1)	-1.5 (± 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 6 in Quality o f Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q (SF)) total score during the randomised treatment period

End point title	Change from randomisation to Week 6 in Quality o f Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q (SF)) total score during the randomised treatment period

End point description:

The original Q-LES-Q is a patient self-rated scale designed to measure the degree of enjoyment and satisfaction experienced by patients in various areas of daily life. It consists of 93 items to measure: physical health, feelings, work, household duties, school, leisure time activities, social relations, and general activities. The Q-LES-Q short form (SF) contains 16 items from the general activities section. Each item is rated on a 5-point scale ranging from 1 (very poor) to 5 (very good).

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	421		
Units: Units on scale				
least squares mean (standard error)	3.5 (± 0.4)	3.2 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation to Week 24 in Q-LES-Q (SF)

End point title	Change from randomisation to Week 24 in Q-LES-Q (SF)

End point description:

The original Q-LES-Q is a patient self-rated scale designed to measure the degree of enjoyment and satisfaction experienced by patients in various areas of daily life. It consists of 93 items to measure: physical health, feelings, work, household duties, school, leisure time activities, social relations, and general activities. The Q-LES-Q short form (SF) contains 16 items from the general activities section. Each item is rated on a 5-point scale ranging from 1 (very poor) to 5 (very good).

End point type	Secondary

End point timeframe:

From randomisation to end of Period B (24 weeks)

End point values	Period B, Placebo and ADT (24 weeks randomised treatment)	Period B, Brexpiprazole and ADT (24 weeks randomised treatm.)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	333		
Units: Units on a scale				
least squares mean (standard error)	7.7 (± 0.7)	6.2 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Randomisation to end of study (28 weeks)	
Adverse event reporting additional description:	
Treatment-emergent adverse events are reported in this section	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Period B, Brexpiprazole + ADT
Reporting group description:	
Brexpiprazole + ADT	
Reporting group title	Period B, Placebo + ADT
Reporting group description:	
Placebo + ADT	

Serious adverse events	Period B, Brexpiprazole + ADT	Period B, Placebo + ADT	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 444 (2.03%)	13 / 441 (2.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
False positive investigation result			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
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			
Forearm fracture			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 444 (0.00%)	2 / 441 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Family stress			

subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed[1]	0 / 307 (0.00%)	1 / 302 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 444 (0.23%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self injurious behaviour			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	2 / 444 (0.45%)	3 / 441 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			

subjects affected / exposed	0 / 444 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 444 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This AE is only applicable for women

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

Non-serious adverse events	Period B, Brexpiprazole + ADT	Period B, Placebo + ADT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 444 (24.32%)	97 / 441 (22.00%)	
Investigations			
Weight increased			
subjects affected / exposed	42 / 444 (9.46%)	22 / 441 (4.99%)	
occurrences (all)	42	22	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	27 / 444 (6.08%)	25 / 441 (5.67%)	
occurrences (all)	42	47	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 444 (7.66%)	31 / 441 (7.03%)	
occurrences (all)	58	42	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 444 (6.31%)	34 / 441 (7.71%)	
occurrences (all)	28	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2013	The time frame for ECG re-evaluation in case of abnormalities was shortened to ensure patient safety. Exclusion criteria 34 and 35: the definition of unstable cardiovascular disease for exclusion was clarified. Antidepressant treatment: it was clarified that patients could continue on the ADT they had received prior to/at screening if they had been treated with this ADT for <6 weeks and had not responded to this ADT.
12 June 2014	The randomisation time point at Week 10 was deleted and all eligible patients were randomised at Week 8. Period C was deleted. As a consequence of this, the total study duration was reduced from 40 to 36 weeks. Early responders to ADT treatment were withdrawn at the Week 6 visit because they were not the target population for this study. The randomisation criteria for Period B were modified to improve the randomisation rate without compromising the study outcome: The patient was required to have a MADRS total score ≥18 instead of ≥20 at the randomisation visit. The criterion "CGI-S score ≥4 at every visit in Period A" was deleted. To obtain the required number of randomised patients, the planned number of screened patients was increased from 1950 to 2924 patients and the planned number of enrolled patients was increased from 1462 to 2193 patients.
07 April 2015	Data monitoring (blinded data) showed that the overall rate of full remission was lower than expected. To maintain the power of the study under the same effect size assumptions, the randomised sample size was increased from 658 to 868 patients. Due to the high number of sites in the study, the site factor was replaced with a country factor in the primary efficacy analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported