Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Fixed-dose Brexpiprazole (OPC-34712) as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder With and Without Anxious Distress

Summary

EudraCT number	2014-000062-22
Trial protocol	DE SK HU PL
Global end of trial date	20 May 2016

Results information

Result version number	v1 (current)
This version publication date	13 July 2017
First version publication date	13 July 2017

Trial information

Trial identification

Sponsor protocol code	331-13-214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02196506
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 103,958

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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	20 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2016
Global end of trial reached?	Yes
Global end of trial date	20 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of brexpiprazole (2.0 mg/day) to placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in subjects who demonstrate an inadequate response to a prospective 8-week trial of the same assigned open-label ADT.

Protection of trial subjects:

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) for each investigational site or country, as appropriate, prior to trial start or prior to implementation of the amendment at that site or country. This trial was conducted in compliance with the protocol, ICH GCP and applicable local laws, and regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 506
Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Slovakia: 77
Country: Number of subjects enrolled	Germany: 95
Country: Number of subjects enrolled	Hungary: 64
Worldwide total number of subjects	837
EEA total number of subjects	331

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)	830
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 837 subjects at 51 trial sites in the following 5 countries: Germany, Hungary, Poland, Slovakia, and United States (US). Total of 1144 subjects with major depressive disorder were screened for the trial, 837 enrolled into Phase A, 394 were randomized into Phase B and 322 continued treatment with placebo+ADT in Phase A+.

Pre-assignment

Screening details:

Trial consisted of a screening phase and 3 phases. In phase A (8-week single-blind prospective treatment phase) and continued treatment in phase A+ (Single-blind phase A Responder), there was single treatment group. In phase B (6-week double-blind randomization phase), there were 2 treatment groups. All Outcome Measures were assessed in phase B.

Period 1

Period 1 title	Phase A
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Arm title	ALL ADT

Arm description:

Subjects meeting entrance criteria who were experiencing a major depressive episode with a HAM-D17 Total Score of greater than or equal 18 at baseline were enrolled into an 8-week Single-blind Prospective Treatment Phase (Phase A). All subjects received single-blind placebo plus an investigator determined, open-label, ADT (antidepressant therapy). Once assigned to an ADT by the investigator, subjects remained on the same ADT for the duration of the trial. At the Week 8 visit, the IWRS (Interactive web response system) determined based on scores entered by the investigator, whether a subject was a "Phase A Responder" or a "Phase A Inadequate Responder."

Arm type	Experimental
Investigational medicinal product name	Escitalopram (Lexapro) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

Investigational medicinal product name	Paroxetine (Paxil CR) controlled-release (CR) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

Investigational medicinal product name	Duloxetine (Cymbalta) delayed-release capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

Investigational medicinal product name	Venlafaxine XR (Effexor XR) extended-release (XR) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

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

Dosage and administration details:

1 tablet along with ADT

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Phase A is a 8-week Single-blind Prospective Treatment Phase during which all subjects received single-blind placebo plus an investigator determined, open-label, ADT.

Number of subjects in period 1	ALL ADT
Started	837
Completed	716
Not completed	121
Consent withdrawn by subject	34
Subject Was Withdrawn By the investigator	10
Adverse Events	22
Subject Met Withdrawal Criteria	34
Lost to follow-up	9
Protocol deviation	12

Period 2

Period 2 title	Phase B
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	2mg Brex+ADT

Arm description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

Arm type	Experimental
Investigational medicinal product name	Escitalopram (Lexapro) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

Investigational medicinal product name	Paroxetine (Paxil CR) controlled-release (CR) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

Investigational medicinal product name	Duloxetine (Cymbalta) delayed-release capsules
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

Investigational medicinal product name	Venlafaxine XR (Effexor XR) extended-release (XR) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

Investigational medicinal product name	Brexpiprazole 2.0 mg/day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/day in week 8, 1 mg/day in week 9, 2.0 mg/day from week 10 to week 13.

Arm title	Placebo+ADT

Arm description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

Arm type	Placebo
Investigational medicinal product name	Escitalopram (Lexapro) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

Investigational medicinal product name	Paroxetine (Paxil CR) controlled-release (CR) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

Investigational medicinal product name	Duloxetine (Cymbalta) delayed-release capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

Investigational medicinal product name	Venlafaxine XR (Effexor XR) extended-release (XR) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

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

Dosage and administration details:

1 tablet along with ADT

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 (Phase B) is the baseline period for this study.

Number of subjects in period 2[3][4]	2mg Brex+ADT	Placebo+ADT
Started	192	202
Completed	177	196
Not completed	15	6
Consent withdrawn by subject	8	1
Adverse Events	4	1
Lost to follow-up	2	1
Subject Met Withdrawal Criteria	-	1
Lack of efficacy	1	2

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Period 2 (Phase B) is the baseline period for this study. A total of 1144 subjects were

screened for this trial and 837 subjects enrolled into Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.
[4] - 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: A total of 1144 subjects were screened for this trial and 837 subjects enrolled into Phase A. A total of 837 subjects received at least 1 dose of ADT during Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.

Period 3

Period 3 title	Phase A +
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[5]

Arms

Arm title	ALL ADT

Arm description:

Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Treatment response in Phase A was determined at the Week 8 visit based on improvement or lack of improvement of the subject's depressive symptoms, which was confirmed by clinical criteria that prospectively defined response. Subject response was determined from clinical data that were entered into the IWRS at each visit. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks, and attended visits at Weeks 11 and 14.

Arm type	Experimental
Investigational medicinal product name	Escitalopram (Lexapro) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

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

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

Investigational medicinal product name	Paroxetine (Paxil CR) controlled-release (CR) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

Investigational medicinal product name	Sertraline (Zoloft) tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

Investigational medicinal product name	Duloxetine (Cymbalta) delayed-release capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

Investigational medicinal product name	Venlafaxine XR (Effexor XR) extended-release (XR) capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

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

Dosage and administration details:

1 tablet along with ADT

Notes:

[5] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks.

Number of subjects in period 3[6]	ALL ADT
Started	322
Completed	308
Not completed	14
Consent withdrawn by subject	5
Subject Was Withdrawn By the investigator	1
Adverse Events	1
Lost to follow-up	6
Subject Met Withdrawal Criteria	1

Notes:

[6] - 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: A total of 1144 subjects were screened for this trial and 837 subjects enrolled into Phase A. A total of 837 subjects received at least 1 dose of ADT during Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to

double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.

Baseline characteristics

Reporting groups

Reporting group title	2mg Brex+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

Reporting group title	Placebo+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

Reporting group values	2mg Brex+ADT	Placebo+ADT	Total
Number of subjects	192	202	394
Age categorical			
Baseline measures are based on the subjects from the Double-blind Placebo-controlled Phase			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	192	200	392
From 65-84 years	0	2	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	43	42.7	
standard deviation	± 12.7	± 12.5	-
Gender categorical			
Units: Subjects			
Female	147	144	291
Male	45	58	103
Type of Episode [n (%)]			
Units: Subjects			
Single Episode	32	35	67
Recurrent Episode	160	167	327
Duration of Current Episode (Months)			
Units: Months			
arithmetic mean	13.3	19.4	
standard deviation	± 14.2	± 46.8	-

Number of Lifetime Episodes			
Units: Number			
arithmetic mean	3.1	3.2	
standard deviation	± 1.8	± 2.4	-

End points

End points reporting groups

Reporting group title	ALL ADT

Reporting group description:

Subjects meeting entrance criteria who were experiencing a major depressive episode with a HAM-D17 Total Score of greater than or equal 18 at baseline were enrolled into an 8-week Single-blind Prospective Treatment Phase (Phase A). All subjects received single-blind placebo plus an investigator determined, open-label, ADT (antidepressant therapy). Once assigned to an ADT by the investigator, subjects remained on the same ADT for the duration of the trial. At the Week 8 visit, the IWRS (Interactive web response system) determined based on scores entered by the investigator, whether a subject was a "Phase A Responder" or a "Phase A Inadequate Responder."

Reporting group title	2mg Brex+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

Reporting group title	Placebo+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

Reporting group title	ALL ADT

Reporting group description:

Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Treatment response in Phase A was determined at the Week 8 visit based on improvement or lack of improvement of the subject's depressive symptoms, which was confirmed by clinical criteria that prospectively defined response. Subject response was determined from clinical data that were entered into the IWRS at each visit. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks, and attended visits at Weeks 11 and 14.

Primary: Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point description:

The MADRS was utilized as the primary efficacy assessment of the subject's level of depression and was administered utilizing the Structured Interview Guide for the MADRS (SIGMA). Detailed instructions for administration of this structured interview was provided in the SIGMA. The MADRS consisted of 10 items each with 7 defined grades of severity. The rating was based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allowed a precise rating of severity. The rater decided whether the rating lied on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5). The 10 items were Apparent sadness, Reported sadness, Inner tension, Reduced sleep, Reduced appetite, Concentration difficulties, Lassitude, Inability to feel, Pessimistic thoughts, Suicidal thoughts.

End point type	Primary

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14

End point values	2mg Brex+ADT	Placebo+ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	202		
Units: Participants				
least squares mean (standard error)	-10.4 (± 0.63)	-8.07 (± 0.61)		

Statistical analyses

Statistical analysis title	Statistical analysis At Week 14
Comparison groups	2mg Brex+ADT v Placebo+ADT
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	-0.62

Notes:

[1] - Comparison between treatment groups was carried out using MMRM (Mixed-model repeated measures), with trial site, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate.

Secondary: Change from Baseline (end of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Score for the Efficacy Sample

End point title	Change from Baseline (end of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Score for the Efficacy Sample

End point description:

The SDS was a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. The SDS was a visual analogue scale that used spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess disability across the 3 domains. The number most representative of how much each area was disrupted by symptoms was marked along the line from 0 = not at all, to 10 = extremely. Scores of 5 and above were associated with significant functional impairment. In addition to the visual scale, the SDS included 2 questions related to productivity losses due to the psychiatric symptoms and impairment.

End point type	Secondary

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14

End point values	2mg Brex+ADT	Placebo+ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	200		
Units: Participants				
least squares mean (standard error)	-1.63 (± 0.18)	-1.41 (± 0.17)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Change At Week 14
Comparison groups	2mg Brex+ADT v Placebo+ADT
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3331 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.23

Notes:

[2] - Comparison between treatment groups was carried out using MMRM, with trial site, treatment group, visit, and treatment.group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

Secondary: Change from Baseline (End of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with < 25% improvement from baseline of Phase A (Week 0) to end of Phase A (Week 8) in MADRS Total Score

End point title	Change from Baseline (End of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with < 25% improvement from baseline of Phase A (Week 0) to end of Phase A (Week 8) in MADRS Total Score

End point description:

The MADRS was utilized as the efficacy assessment of the subject’s level of depression and was administered utilizing the Structured Interview Guide for the MADRS (SIGMA). Detailed instructions for administration of this structured interview was provided in the SIGMA. The MADRS consisted of 10 items each with 7 defined grades of severity.

End point type	Secondary

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14

End point values	2mg Brex+ADT	Placebo+ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	158		
Units: Participants				
least squares mean (standard error)	-11.1 (± 0.71)	-8.87 (± 0.71)		

Statistical analyses

Statistical analysis title	Statistical Analysis At Week 14
Comparison groups	2mg Brex+ADT v Placebo+ADT
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0263 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.23
upper limit	-0.27

Notes:

[3] - Comparison between treatment groups was carried out using MMRM, with treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

Secondary: Change from Baseline (End of Phase A [Week 8]) to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with anxious distress as specified in DSM-V.

End point title	Change from Baseline (End of Phase A [Week 8]) to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with anxious distress as specified in DSM-V.

End point description:

To assess the change From End of Phase A to End of Phase B in MADRS Total Score for the Subpopulations With Anxious Distress as Specified in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).

End point type	Secondary

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14

End point values	2mg Brex+ADT	Placebo+ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	124		
Units: Participants				
least squares mean (standard error)	-11.8 (± 0.81)	-8.87 (± 0.81)		

Statistical analyses

Statistical analysis title	Statistical Analysis At Week 14
Comparison groups	2mg Brex+ADT v Placebo+ADT
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0099 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.24
upper limit	-0.72

Notes:

[4] - Comparison between treatment groups was carried out using MMRM, with treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	2mg Brex+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

Reporting group title	Placebo+ADT

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

Serious adverse events	2mg Brex+ADT	Placebo+ADT	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 192 (0.52%)	0 / 202 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 192 (0.52%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	2mg Brex+ADT	Placebo+ADT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 192 (25.52%)	35 / 202 (17.33%)	

Investigations Weight increased subjects affected / exposed occurrences (all)	 10 / 192 (5.21%) 10	 1 / 202 (0.50%) 1	
Nervous system disorders Akathisia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 16 / 192 (8.33%) 17 7 / 192 (3.65%) 7	 10 / 202 (4.95%) 12 15 / 202 (7.43%) 24	
Psychiatric disorders Restlessness subjects affected / exposed occurrences (all)	 16 / 192 (8.33%) 16	 4 / 202 (1.98%) 4	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 10 / 192 (5.21%) 11	 10 / 202 (4.95%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2014	Amendment 1: Updated the title of the study to include one of the prespecified populations and changing the Director of Clinical Management. Added additional analyses for prespecified populations; specifically: Subjects who showed minimal improvement in Phase A of the trial (< 25% improvement from baseline of Phase A [Week 0] to end of Phase A [Week 8 visit] on MADRS Total Score). Subjects with anxious distress as specified in DSM-V.
15 August 2014	Amendment 2: Changes were made to text because rollover to the open-label extension trial following participation in this trial was no longer available to subjects. The open-label extension trial was no longer allowing subjects to rollover because it had already exceeded the requirement for long-term exposure as defined by the International Conference on Harmonisation guidance (ICH E1A).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported