Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Two Fixed Doses of OPC-34712 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder, the Polaris Trial.

Summary

EudraCT number	2011-001349-33
Trial protocol	DE HU
Global end of trial date	12 September 2013

Results information

Result version number	v1 (current)
This version publication date	02 July 2016
First version publication date	02 July 2016

Trial information

Trial identification

Sponsor protocol code	331-10-227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01360632
WHO universal trial number (UTN)	-
Other trial identifiers	IND No. : 103,958

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, Maryland 20850
Public contact	Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com
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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	04 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2013
Global end of trial reached?	Yes
Global end of trial date	12 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of OPC-34712 (1.0 and 3.0 milligrams (mg)/day) to placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in participants who demonstrated an incomplete response after 8 weeks of prospective treatment with the same assigned open-label ADT.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

Background therapy:

At enrollment the physician carefully considered the participants's antidepressant treatment (ADT) history and made an ADT assignment for each enrolled participant from the following list of sponsor-provided ADTs: escitalopram, fluoxetine, paroxetine controlled release (CR), sertraline, duloxetine, and venlafaxine extended release (XR). Once assigned to one of these ADTs by the physician in Phase A, participants remained on that ADT for the duration of the trial (ie, baseline through Week 14/end of treatment) or were withdrawn if a change in ADT was needed.

Evidence for comparator: -

Actual start date of recruitment	25 June 2011
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	Romania: 12
Country: Number of subjects enrolled	Germany: 77
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Ukraine: 55
Country: Number of subjects enrolled	United States: 442
Worldwide total number of subjects	677
EEA total number of subjects	117

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)	676
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 1539 participants at 92 trial sites in 7 countries. A total of 677 participants were into Phase B (period 2) and 675 received treatment.

Pre-assignment

Screening details:

The study consisted of a 7 to 28-day Screening period, an 8-Week single-blind placebo + ADT prospective Phase-A, a 6-Week double-blind randomization Phase-B or single-blind Phase A+ for those participants who did not meet criteria for randomization and a Follow-up of 30 (+2) days after the last dose of study medication.

Period 1

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

Blinding implementation details:

Treatment assignment code list was available to an independent biostatistician and access to randomized treatment codes restricted to personnel charged with generating/ maintaining randomization files, packaging double-blind treatment, operating interactive voice recognition system and reporting serious adverse events (SAEs) to regulatory agencies. All other trial personnel remained blinded to the identity of the treatment until every participant had completed treatment and the database locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole (1mg) + ADT

Arm description:

Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy).

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	OPC-34712
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole 1mg/day as an adjunctive therapy to an assigned open label ADT.

Arm title	Brexpiprazole (3mg) + ADT

Arm description:

Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	OPC-34712
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

Arm title	Placebo +ADT

Arm description:

Participants were administered placebo daily as an adjunctive therapy to an open label ADT.

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

Dosage and administration details:

Placebo daily as adjunctive therapy to an open label ADT.

Number of subjects in period 1	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT
Started	226	230	221
Completed	216	210	208
Not completed	10	20	13
Consent withdrawn by subject	4	4	7
Physician decision	-	-	1
Met withdrawal criteria	-	2	1
Adverse event	3	9	3
Lost to follow-up	1	1	-
Protocol deviation	1	4	1
Lack of efficacy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole (1mg) + ADT
Reporting group description:	
Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy).	
Reporting group title	Brexpiprazole (3mg) + ADT
Reporting group description:	
Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.	
Reporting group title	Placebo +ADT
Reporting group description:	
Participants were administered placebo daily as an adjunctive therapy to an open label ADT.	

Reporting group values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT
Number of subjects	226	230	221
Age categorical 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)	225	230	221
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.7	44.5	46.6
standard deviation	± 11.6	± 11.2	± 11
Gender categorical Units: Subjects			
Female	158	156	146
Male	68	74	75

Reporting group values	Total		
Number of subjects	677		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	676		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	460		
Male	217		

End points

End points reporting groups

Reporting group title	Brexpiprazole (1mg) + ADT
Reporting group description:	
Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy).	
Reporting group title	Brexpiprazole (3mg) + ADT
Reporting group description:	
Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.	
Reporting group title	Placebo +ADT
Reporting group description:	
Participants were administered placebo daily as an adjunctive therapy to an open label ADT.	
Subject analysis set title	Efficacy Sample
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score in Phase B.	
Subject analysis set title	Efficacy Sample Per Protocol Amendment 3
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.	

Primary: Mean change from the end of Phase A (Week 8 visit) to Phase B (Week 14 visit) in the Montgomery-Asberg Depression Rating Scale for the Efficacy Sample Set

End point title	Mean change from the end of Phase A (Week 8 visit) to Phase B (Week 14 visit) in the Montgomery-Asberg Depression Rating Scale for the Efficacy Sample Set
End point description:	
The MADRS was utilized as the primary efficacy assessment of a participant's level of depression. The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. The MADRS Total Score is the sum of ratings for all 10 items. The possible total scores are from 0 to 60, with higher values indicating worse outcome.	
End point type	Primary
End point timeframe:	
Baseline and Week 14	

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)	-7.65 (± 0.5)	-7.98 (± 0.51)	-6.45 (± 0.51)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0925
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	0.2

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0327
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	-0.13

Primary: Mean Change in MADRS Total Score from Baseline End of Week 8 to Week 14 for the Efficacy Sample per final protocol

End point title	Mean Change in MADRS Total Score from Baseline End of Week 8 to Week 14 for the Efficacy Sample per final protocol

End point description:

The MADRS was utilized as the primary efficacy assessment of a participants level of depression. The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. Analysis was based on all participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Primary

End point timeframe:

Baseline and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)	-7.64 (± 0.52)	-8.29 (± 0.53)	-6.33 (± 0.53)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0737
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	0.13

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	-0.51

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Scores for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Scores for the Efficacy Sample Set

End point description:

This is the key secondary outcome measure. The SDS was a self-rated instrument used to measure the effect of the participants symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores ranged from 0 through 10. 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. For the work/school item, no response was to be entered if the participant did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS score were calculated over the three item scores. All three item scores were needed to be available with the exception of the work/school item score when this item was not applicable. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation.

End point type	Secondary

End point timeframe:

Week 11 and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)				
Week 11	-1.13 (± 0.13)	-0.67 (± 0.13)	-0.58 (± 0.11)	
Week 14	-1.33 (± 0.14)	-1.21 (± 0.13)	-0.84 (± 0.13)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.12

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0474
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0

Statistical analysis title	Statistical analysis 3 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.23

Statistical analysis title	Statistical analysis 4 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5792
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.23

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in SDS Mean Scores for the Efficacy Sample per final protocol

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in SDS Mean Scores for the Efficacy Sample per final protocol

End point description:

The SDS was a self-rated instrument used to measure the effect of the participants symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores ranged from 0 through 10. 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. For the work/school item, no response was to be entered if the participant did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS score were calculated over the three item scores. All three item scores were needed to be available with the exception of the work/school item score when this item was not applicable. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 11 and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)				
Week 11	-1.11 (± 0.13)	-0.74 (± 0.13)	-0.53 (± 0.14)	
Week 14	-1.27 (± 0.15)	-1.26 (± 0.15)	-0.78 (± 0.15)	

Statistical analyses

Statistical analysis title	Statisical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0158
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	-0.09

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0191
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.08

Statistical analysis title	Statistical analysis 3 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.22

Statistical analysis title	Statistical analysis 4 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial

site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2627
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.15

Secondary: Mean change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample Set

End point description:

The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 8 to Week 13

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N= 222, 221, 214)	-3.25 (± 0.3)	-2.53 (± 0.3)	-2.19 (± 0.31)	
Week 10 (N= 222, 221, 213)	-5.34 (± 0.38)	-4.8 (± 0.38)	-3.91 (± 0.39)	
Week 11 (N= 221, 218, 213)	-6.25 (± 0.41)	-5.56 (± 0.41)	-4.85 (± 0.41)	
Week 12 (N= 216, 213, 210)	-7.08 (± 0.43)	-6.8 (± 0.44)	-5.52 (± 0.44)	
Week 13 (N= 213, 212, 204)	-7.55 (± 0.46)	-7.73 (± 0.46)	-6.02 (± 0.47)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	-0.26

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4137
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	0.47

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.47
upper limit	-0.4

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0914 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	0.14

Notes:

[1] - MMRM method with an unstructured variance covariance matrix was used, with model terms trial site, treatment group, visit, treatment group-by-visit and Baseline-by-visit interaction.

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0139
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.28

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2097
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	0.4

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0099
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-0.38

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	-0.1

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0177
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-0.27

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-0.44

Secondary: Mean Change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample per final protocol

End point title	Mean Change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample per final protocol

End point description:

The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3

End point type	Secondary

End point timeframe:

Week 8 to Week 13

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N=208, 210, 199)	-3.09 (± 0.31)	-2.6 (± 0.31)	-2.18 (± 0.32)	
Week 10 (N=208, 208, 199)	-5.12 (± 0.39)	-4.92 (± 0.39)	-3.95 (± 0.4)	
Week 11 (N=207, 205, 199)	-6.22 (± 0.42)	-5.76 (± 0.43)	-4.86 (± 0.43)	
Week 12 (N=203, 202, 195)	-7.09 (± 0.45)	-7.11 (± 0.45)	-5.48 (± 0.46)	
Week 13 (N=200, 199, 191)	-7.56 (± 0.47)	-8.05 (± 0.48)	-5.93 (± 0.49)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured

variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	-0.1

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.4

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0313
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	-0.11

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0732
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	0.09

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	-0.21

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1233
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	0.25

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.39

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0092
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	-0.41

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0139
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	-0.33

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	-0.81

Secondary: Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B in Clinical Global Impression Severity of Illness (CGI-S) for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B in Clinical Global Impression Severity of Illness (CGI-S) for the Efficacy Sample Set

End point description:

The severity of illness for each participant was rated using the CGI-S. To perform this assessment, the study physician had to answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N= 222, 221, 214)	-0.25 (± 0.03)	-0.22 (± 0.03)	-0.16 (± 0.03)	
Week 10 (N= 222, 221, 213)	-0.52 (± 0.05)	-0.46 (± 0.05)	-0.31 (± 0.05)	
Week 11 (N= 221, 218, 213)	-0.64 (± 0.05)	-0.51 (± 0.05)	-0.44 (± 0.05)	
Week 12 (N= 216, 213, 210)	-0.73 (± 0.05)	-0.72 (± 0.05)	-0.59 (± 0.05)	
Week 13 (N= 213, 212, 204)	-0.78 (± 0.06)	-0.77 (± 0.06)	-0.66 (± 0.06)	
Week 14 (N= 216, 208, 207)	-0.86 (± 0.06)	-0.9 (± 0.06)	-0.75 (± 0.06)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0436
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1741
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.03

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.08

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0266
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.02

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	-0.07

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3053
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.06

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0541
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0912
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.02

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1553
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.04

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1855
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.05

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.06

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0852
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.02

Secondary: Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B Week in Clinical CGI-S for the Efficacy Sample per final protocol

End point title	Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B Week in Clinical CGI-S for the Efficacy Sample per final protocol

End point description:

The severity of illness for each participant was rated using the CGI-S. To perform this assessment, the study physician had to answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N=208, 210,199)	-0.24 (± 0.03)	-0.23 (± 0.03)	-0.16 (± 0.03)	
Week 10 (N=208, 208, 199)	-0.5 (± 0.05)	-0.47 (± 0.05)	-0.33 (± 0.05)	
Week 11 (N=207, 205, 199)	-0.64 (± 0.05)	-0.53 (± 0.05)	-0.45 (± 0.05)	
Week 12 (N=203, 202, 195)	-0.73 (± 0.06)	-0.74 (± 0.06)	-0.58 (± 0.06)	
Week 13 (N=200, 199, 191)	-0.77 (± 0.06)	-0.8 (± 0.06)	-0.64 (± 0.06)	
Week 14 (N=204, 196, 193)	-0.87 (± 0.06)	-0.92 (± 0.06)	-0.72 (± 0.06)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0817
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.01

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1406
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.02

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.04

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0287
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.02

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0071
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	-0.05

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2503
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.06

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0539
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0398
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.01

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1168
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.03

Statistical analysis title	Statistical anaysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0621
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.01

Statistical analysis title	Statisical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.02

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0213
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.03

Secondary: Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in Inventory of Depressive Symptomatology (Self-Report) IDS-SR Total Score for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in Inventory of Depressive Symptomatology (Self-Report) IDS-SR Total Score for the Efficacy Sample Set

End point description:

IDS-SR was a 30-item self-report measured to assess core diagnostic depressive symptoms and atypical and melancholic symptom features of major depressive disorders. The IDS-SR consists of 30 items, all rated on a 0 to 3 scale with 0 being the "best" rating and 3 being the "worst" rating. Besides item 9, two sub-items 9A and 9B exist, with possible scores of 1, 2 or 3 for item 9A, and 0 or 1 for item 9B. The scores for these two sub-items were not included in the calculation of the total score. The IDS-SR Total Score was the sum of ratings of 28 item scores. The possible IDSSR Total Score ranged from 0 to 84. The IDS-SR Total Score was un-evaluable if less than 23 of the 28 items were recorded. If the number of items recorded was at least 23 and at most 27, the IDS-SR Total Score was the mean of the recorded items multiplied by 28, and was then rounded off to the first decimal place.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N= 222, 221, 214)	-3.58 (± 0.41)	-2.68 (± 0.42)	-2.31 (± 0.42)	
Week 10 (N= 222, 221, 213)	-4.97 (± 0.49)	-4 (± 0.5)	-3.11 (± 0.5)	
Week 11 (N= 220, 218, 213)	-5.83 (± 0.56)	-4.15 (± 0.56)	-3.74 (± 0.57)	
Week 12 (N= 216, 213, 210)	-6.33 (± 0.59)	-5.77 (± 0.59)	-4.43 (± 0.6)	
Week 13 (N= 213, 212, 204)	-6.96 (± 0.63)	-6.62 (± 0.63)	-5.66 (± 0.64)	
Week 14 (N= 216, 208, 207)	-7.02 (± 0.66)	-6.94 (± 0.66)	-5.42 (± 0.67)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0228
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.37
upper limit	-0.18

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5081
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.73

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.53

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1898
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	0.44

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	-0.56

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5935
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	1.11

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0211
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.52
upper limit	-0.29

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1031
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	0.27

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1366
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.02
upper limit	0.41

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2709
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	0.75

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0812
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.2

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	0.29

Secondary: Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in IDS-SR Total Score for the Efficacy Sample per final protocol

End point title	Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in IDS-SR Total Score for the Efficacy Sample per final protocol

End point description:

The IDS-SR was a 30-item self-report measured to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of major depressive disorders. The IDS-SR consists of 30 items, all rated on a 0 to 3 scale with 0 being the “best” rating and 3 being the “worst” rating. Besides

item 9, two sub-items 9A and 9B exist, with possible scores of 1, 2 or 3 for item 9A, and 0 or 1 for item 9B. The scores for these two sub-items were not included in the calculation of the total score. The IDS-SR Total Score was the sum of ratings of 28 item scores. The possible IDSSR Total Score ranged from 0 to 84. The IDS-SR Total Score was un-evaluable if less than 23 of the 28 items were recorded. If the number of items recorded was at least 23 and at most 27, the IDS-SR Total Score was the mean of the recorded items multiplied by 28, and was then rounded off to the first decimal place.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)				
Week 9 (N=208, 210, 199)	-3.27 (± 0.42)	-2.65 (± 0.42)	-2.15 (± 0.43)	
Week 10 (N=208, 209, 199)	-4.7 (± 0.51)	-4.13 (± 0.51)	-2.94 (± 0.52)	
Week 11 (N=206, 205, 199)	-5.77 (± 0.57)	-4.29 (± 0.58)	-3.46 (± 0.59)	
Week 12 (N=203, 202, 195)	-6.33 (± 0.61)	-6.05 (± 0.61)	-4.18 (± 0.63)	
Week 13 (N=200, 199, 191)	-6.88 (± 0.64)	-6.97 (± 0.64)	-5.25 (± 0.66)	
Week 14 (N=204, 196, 193)	-6.97 (± 0.67)	-7.2 (± 0.68)	-5.07 (± 0.69)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0496
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	0

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	0.63

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0125
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	-0.38

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0898
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	0.19

Statistical analysis title	Statitical analysis 1 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	-0.74

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	0.74

Notes:

[2] - MMRM method with an unstructured variance covariance matrix was used, with model terms trial site, treatment group, visit, treatment group-by-visit and Baseline-by-visit interaction.

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.82
upper limit	-0.48

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0287
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	-0.19

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0686
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	0.12

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	0.04

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0448
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	-0.04

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0251
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	-0.27

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) Hamilton Depression Scale 17 Item Version (HAM)-D17 Total Score for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) Hamilton Depression Scale 17 Item Version (HAM)-D17 Total Score for the Efficacy Sample Set

End point description:

The HAM-D17 was utilized as a secondary assessment of a participants level of depression. The HAM-D (17-Item) consisted of 17 items. Eight items were rated on a 0 to 2 scale (items 4, 5, 6, 12, 13, 14, 16 and 17), while nine items (items 1, 2, 3, 7, 8, 9, 10, 11, and 15) were rated on a 0 to 4 scale (twice the weight of the other items). For all of these items, 0 was the "best" rating and the highest score (2 or 4) was the "worst" rating. The possible total scores were from 0 to 52. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	220	213	
Units: Units on a scale				
least squares mean (standard error)	-5.47 (± 0.36)	-6.14 (± 0.36)	-4.8 (± 0.37)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The last observation carried forward (LOCF) method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1732 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	0.29

Notes:

[3] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.31
upper limit	-0.37

Notes:

[4] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-D17 Total Score for the Efficacy Sample Set per final protocol

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-D17 Total Score for the Efficacy Sample Set per final protocol

End point description:

The HAM-D17 was utilized as a secondary assessment of a participants level of depression. The HAM-D (17-Item) consisted of 17 items. Eight items were rated on a 0 to 2 scale (items 4, 5, 6, 12, 13, 14, 16 and 17), while nine items (items 1, 2, 3, 7, 8, 9, 10, 11, and 15) were rated on a 0 to 4 scale (twice the weight of the other items). For all of these items, 0 was the "best" rating and the highest score (2 or 4) was the "worst" rating. The possible total scores were from 0 to 52. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208	207	198	
Units: Units on a scale				
least squares mean (standard error)	-5.36 (± 0.37)	-6.26 (± 0.38)	-4.57 (± 0.39)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1226 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	0.21

Notes:

[5] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.69
upper limit	-0.68

Notes:

[6] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Hamilton Anxiety Rating Scale (HAM-A) Total Score for the Efficacy Sample Set

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Hamilton Anxiety Rating Scale (HAM-A) Total Score for the Efficacy Sample Set

End point description:

The HAM-A is utilized for the evaluation of anxiety symptoms. The HAM-A consists of 14 items. Each item is rated on a 0 to 4 scale. For all of these items, 0 is the "best" rating and 4 is the "worst" rating. If no item scores are missing, then the HAM-A total score is the sum of all 14 item scores. The possible total scores are from 0 to 56. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	220	216	210	
Units: Units on a scale				
least squares mean (standard error)	-3.43 (± 0.31)	-3.89 (± 0.31)	-3.33 (± 0.32)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8164 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	0.73

Notes:

[7] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1939 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	0.28

Notes:

[8] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariate

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-A Total for the Efficacy Sample per final protocol

End point title	Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-A Total for the Efficacy Sample per final protocol

End point description:

The HAM-A is utilized for the evaluation of anxiety symptoms. The HAM-A consists of 14 items. Each item is rated on a 0 to 4 scale. For all of these items, 0 is the "best" rating and 4 is the "worst" rating. If no item scores are missing, then the HAM-A total score is the sum of all 14 item scores. The possible total scores are from 0 to 56. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	206	204	195	
Units: Units on a scale				
least squares mean (standard error)	-3.35 (± 0.32)	-3.96 (± 0.33)	-3.07 (± 0.33)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5192 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	0.57

Notes:

[9] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0443 [10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	-0.02

Notes:

[10] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample Set

End point title	Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample Set

End point description:

The efficacy of study medication was rated for each participant using the CGI-I. The study physician would rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 9 (N= 222, 221, 214)	3.36 (± 0.68)	3.4 (± 0.75)	3.51 (± 0.67)	
Week 10 (N= 225, 226, 218)	3.08 (± 0.85)	3.09 (± 0.85)	3.34 (± 0.85)	
Week 11 (N= 225, 226, 218)	2.91 (± 0.82)	2.99 (± 0.89)	3.17 (± 0.88)	
Week 12 (N= 225, 226, 218)	2.78 (± 0.87)	2.81 (± 0.95)	3.02 (± 0.95)	
Week 13 (N= 225, 226, 218)	2.72 (± 0.87)	2.73 (± 1.01)	2.97 (± 1)	
Week 14 (N= 225, 226, 218)	2.69 (± 0.89)	2.66 (± 1.1)	2.85 (± 1.01)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0248 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.02

Notes:

[11] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1334 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.03

Notes:

[12] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statisitcal analysis 1 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.11

Notes:

[13] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statisitcal analysis 2 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.09

Notes:

[14] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.11

Notes:

[15] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

Statistical analysis title	Statisitcal analysis 2 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0254 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.02

Notes:

[16] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.08

Notes:

[17] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0152 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.04

Notes:

[18] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.08

Notes:

[19] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.05

Notes:

[20] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Statisitical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0755 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.02

Notes:

[21] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0527 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0

Notes:

[22] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

Secondary: Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample per final protocol

End point title	Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample per final protocol

End point description:

The efficacy of study medication was rated for each participant using the CGI-I. The study physician would rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 9 (N=208, 210, 199)	3.39 (± 0.65)	3.42 (± 0.74)	3.54 (± 0.65)	
Week 10 (N=211, 213, 203)	3.1 (± 0.82)	3.08 (± 0.84)	3.35 (± 0.84)	
Week 11 (N=211, 213, 203)	2.93 (± 0.8)	2.99 (± 0.89)	3.19 (± 0.86)	
Week 12 (N=211, 213, 203)	2.8 (± 0.86)	2.81 (± 0.94)	3.06 (± 0.94)	
Week 13 (N=211, 213, 203)	2.75 (± 0.86)	2.72 (± 1)	3.01 (± 0.96)	
Week 14 (N=211, 213, 203)	2.71 (± 0.88)	2.65 (± 1.09)	2.9 (± 0.99)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0275 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.01

Notes:

[23] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statisitcal analysis 2 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1583 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.04

Notes:

[24] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.09

Notes:

[25] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.09

Notes:

[26] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [27]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.11

Notes:

[27] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.1

Notes:

[28] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111 [29]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.05

Notes:

[29] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.09

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046 [30]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.09

Notes:

[30] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0237 [31]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.03

Notes:

[31] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0171 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.04

Notes:

[32] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0235 [33]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.03

Notes:

[33] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Secondary: Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set.

End point title	Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set.

End point description:

MADRS response was defined as >=50 percent reduction in MADRS Total Score from end of Phase A (Week 8). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	221	214	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N= 222, 221, 214)	4.5	0.45	2.8	
Week 10 (N= 225, 226, 218)	10.2	6.19	5.05	
Week 11 (N= 225, 226, 218)	13.3	10.6	8.72	
Week 12 (N= 225, 226, 218)	16.9	15.5	10.1	
Week 13 (N= 225, 226, 218)	18.2	18.6	15.6	
Week 14 (N= 225, 226, 218)	23.1	22.1	15.1	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5279
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	3.68

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.94

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0484
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	3.72

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5813
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.5

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1236
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.54

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.
The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4998
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.1

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.61

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0822
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.43

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4049
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.78

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2951
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.8

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0248
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.2

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0326
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.21

Secondary: Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

End point title	Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

End point description:

MADRS response was defined as >=50 percent reduction in MADRS Total Score from end of Phase A (Week 8). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N=208, 210, 199)	3.37	0.48	3.02	
Week 10 (N=211, 213, 203)	7.58	6.1	4.93	
Week 11 (N=211, 213, 203)	13.3	11.3	8.37	
Week 12 (N=211, 213, 203)	16.6	16.4	10.3	
Week 13 (N=211, 213, 203)	18	19.2	14.3	
Week 14 (N=211, 213, 203)	23.2	23	14.3	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9
Statistical analysis description:	
All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.	
Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7993
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.55

Statistical analysis title	Statistical analysis 2 at Week 9
Statistical analysis description:	
All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.	
Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.93

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2825
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	3.16

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6375
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.5

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0923
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.82

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3812
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.3

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0464
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.65

Statistical analysis title	Statistical analysis 2 at Week 12
Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.64

Statistical analysis title	Statistical analysis 1 at Week 13
Statistical analysis description:	
All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.	
Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2124
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.06

Statistical analysis title	Statistical analysis 2 at Week 13
Statistical analysis description:	
All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data	
Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1078
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	2.14

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.5

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0162
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	2.5

Secondary: Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample Set.

End point title	Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample Set.

End point description:

MADRS remission was defined as a < or equal to 10 and > or equal to 50% reduction in MADRS Total Score from end of Phase A (Week 8). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	221	214	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N= 222, 221, 214)	3.15	0.45	2.8	
Week 10 (N= 225, 226, 218)	4	2.65	4.13	
Week 11 (N= 225, 226, 218)	8.44	6.19	5.5	
Week 12 (N= 225, 226, 218)	11.1	8.85	5.96	
Week 13 (N= 225, 226, 218)	10.7	12.8	9.17	
Week 14 (N= 225, 226, 218)	15.1	13.7	11.9	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9498
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	2.9

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.94

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8609
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.17

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2846
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.54

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.99

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7513
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.37

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0554
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	3.35

Statistical analysis title	Statisitcal analysis 2 ar Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2409
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.87

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5538
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.02

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1743
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.41

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2843
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.07

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.92

Secondary: Percentage of participants with a MADRS Remission during Phase B

relative to the end of Phase A (Week 8) for the Efficacy Sample per final protocol	
End point title	Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample per final protocol

End point description:

MADRS remission was defined as a < or equal to 10 and > or equal to 50% reduction in MADRS Total Score from end of Phase A (Week 8). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N=208, 210, 199)	1.92	0.48	3.02	
Week 10 (N=211, 213, 203)	2.37	2.82	3.94	
Week 11 (N=211, 213, 203)	8.06	6.57	5.42	
Week 12 (N=211, 213, 203)	10.4	9.39	6.4	
Week 13 (N=211, 213, 203)	9.95	13.1	8.37	
Week 14 (N=211, 213, 203)	14.7	14.1	10.8	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3867
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.97

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.93

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.66

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3266
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.62

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3027
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	3.1

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.696
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.52

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1368
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	3.07

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2387
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.89

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4498
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.28

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1009
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.82

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1499
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.41

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of remission rate
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.18

Secondary: Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set

End point title	Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set

End point description:

A CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N= 222, 221, 214)	9.46	10.4	6.54	
Week 10 (N= 225, 226, 218)	23.6	23	13.3	

Week 11 (N= 225, 226, 218)	28.4	30.1	21.6	
Week 12 (N= 225, 226, 218)	35.1	38.1	29.4	
Week 13 (N= 225, 226, 218)	40	43.4	28.9	
Week 14 (N= 225, 226, 218)	41.8	47.8	36.7	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2873
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.65

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2677
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.36

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0031
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	2.68

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	2.5

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0665
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.83

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.91

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2224
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.54

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0369
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.68

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0179
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.75

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.89

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3249
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.41

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.66

Secondary: Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

End point title	Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

End point description:

A CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

End point type	Secondary

End point timeframe:

Week 8 to Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Percentage of participants				
number (not applicable)				
Week 9 (N=208, 210, 199)	7.69	9.52	5.53	
Week 10 (N=211, 213, 203)	21.8	23	12.3	
Week 11 (N=211, 213, 203)	27.5	30	19.7	
Week 12 (N=211, 213, 203)	34.1	38	27.6	
Week 13 (N=211, 213, 203)	38.9	44.1	27.1	
Week 14 (N=211, 213, 203)	41.2	48.4	34	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5836
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.49

Statistical analysis title	Statistical analysis 2 at Week 9

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3792
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.37

Statistical analysis title	Statistical analysis 1 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.74

Statistical analysis title	Statistical analysis 2 at Week 10

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	2.63

Statistical analysis title	Statistical analysis 1 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0526
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.99

Statistical analysis title	Statistical analysis 2 at Week 11

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.11

Statistical analysis title	Statistical analysis 1 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1689
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.63

Statistical analysis title	Statistical analysis 2 at Week 12

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0231
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.8

Statistical analysis title	Statistical analysis 1 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0175
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.84

Statistical analysis title	Statistical analysis 2 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	2.07

Statistical analysis title	Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1396
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.55

Statistical analysis title	Statistical analysis 2 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.86

Secondary: Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set

End point title	Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set

End point description:

The SDS is a self-rated instrument used to measure the effect of the patient’s symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0 = not at all, to 10 = extremely. For the work/school item, no response was to be entered if the patient did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS Score will be calculated over the three item scores. All three item scores need to be available with the exception of the work/school item score when this item is not applicable. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

End point type	Secondary
End point timeframe:	
Week 11 and Week 14	

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	226	218	
Units: Units on a scale				
least squares mean (standard error)				
Work/school: Week 11	-1 (± 0.16)	-0.18 (± 0.18)	-0.55 (± 0.15)	
Work/school: Week 14	-1.16 (± 0.17)	-0.91 (± 0.18)	-0.73 (± 0.17)	
Social life: Week 11	-1.13 (± 0.14)	-0.76 (± 0.14)	-0.72 (± 0.14)	
Social life: Week 14	-1.39 (± 0.15)	-1.31 (± 0.15)	-0.91 (± 0.15)	
Family life: Week 11	-1.14 (± 0.14)	-0.74 (± 0.14)	-0.51 (± 0.12)	
Family life: Week 14	-1.35 (± 0.15)	-1.28 (± 0.16)	-0.8 (± 0.15)	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

For Item: Work/School: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0377
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.03

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

For Item: Work/School: Week 14 . The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and

interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0741
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.04

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

For Item: Work/School: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0966
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.81

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

For Item: Work/School: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4774
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.31

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0263
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.05

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0214
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	-0.07

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8281
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.32

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.01

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	-0.26

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0093
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.14

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2182
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.14

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0256
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.06

Secondary: Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set Per Final Protocol

End point title	Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set Per Final Protocol

End point description:

The SDS is a self-rated instrument used to measure the effect of the patient's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0 = not at all, to 10 = extremely. For the work/school item, no response was to be entered if the patient did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS Score will be calculated over the three item

scores. All three item scores need to be available with the exception of the work/school item score when this item is not applicable. All participants in the efficacy sample who met the revised randomization criteria for incomplete response as defined in protocol amendment 3.

End point type	Secondary

End point timeframe:

Week 11 and Week 14

End point values	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	213	203	
Units: Units on a scale				
least squares mean (standard error)				
Work/school: Week 11	-1.01 (± 0.18)	-0.2 (± 0.2)	-0.48 (± 0.19)	
Work/school: Week 14	-1.11 (± 0.2)	-0.93 (± 0.21)	-0.65 (± 0.2)	
Social life: Week 11	-1.11 (± 0.15)	-0.82 (± 0.15)	-0.68 (± 0.15)	
Social life: Week 14	-1.34 (± 0.16)	-1.37 (± 0.16)	-0.88 (± 0.17)	
Family life: Week 11	-1.17 (± 0.14)	-0.89 (± 0.15)	-0.54 (± 0.15)	
Family life: Week 14	-1.32 (± 0.16)	-1.39 (± 0.16)	-0.81 (± 0.16)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Work/school: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0341
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.04

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

School/work: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0816
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.06

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Work/school: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2561
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.78

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Work/school: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2561
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.06

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0331
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.03

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0352
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.03

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.25

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0282
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.05

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.24

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0186
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.09

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (3mg) + ADT v Placebo +ADT
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0824
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.04

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

Comparison groups	Brexpiprazole (1mg) + ADT v Placebo +ADT
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were captured from randomization to double-blind treatment at Week 8, throughout the 6 week double blind phase to Follow-up 30 (+ 2) days after last dose of study medication.

Adverse event reporting additional description:

Safety sample comprised of randomized participants in Phase B who received at least one dose of double-blind trial medication. Participants were excluded only if there was evidence that the participant did not take trial medication. If a participant was dispensed trial medication and is lost to follow-up that participant was considered exposed.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Brexpiprazole (1mg) + ADT

Reporting group description:

Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT.

Reporting group title	Brexpiprazole (3mg) + ADT

Reporting group description:

Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

Reporting group title	Placebo +ADT

Reporting group description:

Participants were administered placebo daily as an adjunctive therapy to an open label ADT.

Serious adverse events	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 226 (0.44%)	1 / 229 (0.44%)	0 / 220 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 229 (0.44%)	0 / 220 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 229 (0.00%)	0 / 220 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Brexpiprazole (1mg) + ADT	Brexpiprazole (3mg) + ADT	Placebo +ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 226 (27.88%)	72 / 229 (31.44%)	29 / 220 (13.18%)
Investigations			
Weight increased			
subjects affected / exposed	15 / 226 (6.64%)	13 / 229 (5.68%)	2 / 220 (0.91%)
occurrences (all)	15	13	2
Nervous system disorders			
Akathisia			
subjects affected / exposed	10 / 226 (4.42%)	31 / 229 (13.54%)	5 / 220 (2.27%)
occurrences (all)	10	35	5
Headache			
subjects affected / exposed	21 / 226 (9.29%)	14 / 229 (6.11%)	17 / 220 (7.73%)
occurrences (all)	24	18	21
Somnolence			
subjects affected / exposed	9 / 226 (3.98%)	13 / 229 (5.68%)	1 / 220 (0.45%)
occurrences (all)	9	15	1
Tremor			
subjects affected / exposed	9 / 226 (3.98%)	12 / 229 (5.24%)	7 / 220 (3.18%)
occurrences (all)	15	16	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 226 (6.64%)	7 / 229 (3.06%)	4 / 220 (1.82%)
occurrences (all)	15	9	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2011	Changed history of inadequate response from "3 or fewer adequate antidepressant treatments" to "at least 1 and no more than 3 adequate antidepressant treatments."; clarified instructions for preparation of whole blood sample for metabolic profiling; made administrative changes and corrected typographical errors.
08 November 2011	Clarified dosing of duloxetine to allow participants to titrate from 30 to 40 mg/day rather than forcing titration from 30 to 60 mg/day; specified that participants taking desvenlafaxine at screening should not be assigned to venlafaxine XR in Phase A; clarified requirements for collection of pharmacogenomic sample to indicate that a sample was not required from participants who withdrew during Phase A. In the protocol, clarified rules for ADT dose adjustment at Week 8 (ie, no change for participants entering Phase B, adjustments permitted for participants entering Phase A+); clarified that the serum pregnancy test was the definitive test for determining pregnancy, irrespective of urine pregnancy test result; added language to the prohibited therapies section to indicate that participants who received electroconvulsive for the current major depressive episode were excluded from the trial; Clarified that participants who were sterile (ie, women who had an oophorectomy and/or hysterectomy or had been postmenopausal for at least 12 consecutive months; or men who had orchidectomy) were not required to use two different methods of birth control; per posting from Food and Drug Administration, added linezolid and methylene blue to list of drugs that could result in serotonin syndrome if co-administered with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitor; made administrative changes.
23 March 2012	Revised statistical method in response to regulatory feedback; based on the review of completed phase 2 data, revised randomization criteria into Phase B, and trial procedures to increase the precision in the estimation of treatment effects: In the original protocol, the primary efficacy analysis used an analysis of covariance (ANCOVA) model based on the last observation carried forward (LOCF) dataset. The mixed models repeated measures (MMRM) model was included as a sensitivity analysis. Based on feedback from the FDA, the primary analysis method was changed to the MMRM model, with the ANCOVA LOCF used as the sensitivity analysis; Score-based criteria for determination of incomplete response for entry into Phase B were amended to better define incomplete responders as those participants who did not show a response at any visit during the single-blind prospective Phase A. Whereas before Protocol Amendment 3 response was assessed only at Week 8, after Protocol Amendment 3 participants who met response criteria at any time during Phase A were excluded from randomization. This change resulted from review of the data from the completed phase 2 trials (331-08-211 and 331-09-222). In addition, the criteria for response and incomplete response were removed from the main protocol to an addendum so that investigators and raters would be blinded to the randomization criteria in order to minimize potential rater inflation of efficacy scale scores. Eligibility for randomization was confirmed by the medical surveillance team from INC Research and/or through preprogrammed calculations made by the Interactive Voice/Web Recognition System using the prospectively defined score-based criteria. No new visits or assessments were added to the conduct of the trial as a result of this amendment. Therefore, the blinded changes to the randomization criteria did not pose any additional risk to trial participants.

23 March 2012	The investigator retained the option not to randomize any participant who met criteria for score-based eligibility, but who, in the investigator's judgment, should not have been randomized due to safety concerns or other reasons; in order to ensure a more even distribution of ADTs across the participant population, individual sites were not permitted to assign more than 2 out of every 6 participants at a site to any one ADT without permission of the medical monitor; item 32 of the exclusion criteria was clarified to exclude any participant who, in the opinion of the investigator or medical monitor, should not participate in the trial; due to the changes implemented in Amendment 3, the number of participants screened and enrolled into Phase A and randomized into Phase B was increased and the enrollment period and overall trial duration were extended 3 months to allow for enrollment of the additional participants in Phase A. The number of sites was reduced from 90 to 63 to minimize variability introduced by inclusion of multiple sites; made administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported