



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo- and Active Comparator-controlled Trial of Flexible-dose Brexpiprazole (OPC-34712) as Adjunctive Therapy in the Treatment of Adults With Major Depressive Disorder, the Delphinus Trial.

Summary

EudraCT number	2012-003948-67
Trial protocol	DE SK FR ES
Global end of trial date	10 November 2016

Results information

Result version number	v1 (current)
This version publication date	26 January 2018
First version publication date	26 January 2018

Trial information

Trial identification

Sponsor protocol code	331-12-282
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization,
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland , United States, 20850
Public contact	Regulatory Project Manager, INC Research, +34 916307400, ricardo.sanz-gadea@incresearch.com
Scientific contact	Regulatory Project Manager, INC Research, +34 916307400, ricardo.sanz-gadea@incresearch.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2016
Global end of trial reached?	Yes
Global end of trial date	10 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of brexpiprazole (flexible dose) with placebo as adjunctive therapy to an assigned openlabel antidepressant therapy (ADT) in the proposed subject population with major depressive disorder (MDD).

Protection of trial subjects:

The study was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, and the applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, any amendments, and the informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) for each investigational site or country, as appropriate, prior to trial start or prior to implementation of the protocol or protocol amendment, if any, at that site and/or country.. Written informed consent (translated in Canadian French, German, French, Russian, Polish, and Serbian) was obtained from all subjects (or their guardian or legal representative, as applicable according to local laws) and was documented prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2012
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	United States: 239
Country: Number of subjects enrolled	Russian Federation: 165
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 34
Worldwide total number of subjects	503
EEA total number of subjects	93

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)	501
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial was conducted at 75 trial sites in 7 countries (United States, Russia, Poland, France, Serbia, Germany & Canada). Of the screened 3001 subjects (with major depressive disorder), 2182 entered Phase A, 503 (non-responders) were randomized into Phase B (brexpiprazole/Seroquel/placebo +ADT) and 1394 entered Phase A+ (continued Phase A therapy)

Pre-assignment

Screening details:

Screening period ranged from a minimum of 7 days to a maximum of 28 days and began when informed consent was signed. The purpose was to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout (minimum of 24 hours) prohibited concomitant pharmacotherapy, if applicable.

Period 1

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

Blinding implementation details:

Investigational medicinal product (placebo, brexpiprazole, or Seroquel XR) other than ADT was double-blind at any given visit. Personnel at trial sites were blinded to details of randomization criteria & dosing schedule. Except in cases of emergency unblinding, subjects, investigational site personnel, sponsor employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every subject had completed trial treatment and the database had been locked

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole + Antidepressant therapy (ADT)

Arm description:

Subjects received orally brexpiprazole 1 mg tablet per day and assigned ADT at randomization, and then the dose was increased to 2 mg/day at Day 7 (\pm 2 days). Subjects remained at the target dose (2 mg/day) unless the investigator requested an increase to a higher dose. Change in the dose was done based on a clinical assessment of the benefit and the subject's tolerance of the investigational medicinal product (IMP). The choice of ADT was determined by considering each subject's antidepressant treatment history.

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

Dosage and administration details:

Orally brexpiprazole 1 mg tablet per day at randomization, and then the dose was increased to 2 mg/day at Day 7 (\pm 2 days).

Arm title	Quetiapine (Seroquel) extended release (XR) + ADT
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Arm description:

Randomized subjects received orally quetiapine XR tablets at a dose of 50 mg/day and assigned ADT therapy on Day 1 and Day 2, and then the dose was increased to 150 mg/day on Day 3 through Day 14. Subjects remained at the target dose (150 mg/day) unless the investigator requested an increase to a higher dose.

Arm type	Active comparator
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Investigational medicinal product name	Quetiapine XR tablet
Investigational medicinal product code	
Other name	Seroquel XR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Orally quetiapine 50 mg XR tablet per day on Day 1 and Day 2, and then the dose was increased to 150 mg/day on Day 3 through Day 14.

Arm title	Placebo + ADT
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Arm description:

Randomized subjects received orally brexpiprazole or quetiapine matching placebo tablets with the open-label ADT (Phase A) at the final dose reached during the prospective treatment phase.

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:

Orally brexpiprazole or quetiapine matching placebo tablets with the open-label ADT final dose reached during the prospective treatment phase (Phase A).

Number of subjects in period 1	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT
Started	197	100	206
Completed	171	86	186
Not completed	26	14	20
Adverse events	2	4	2
Subject met protocol specified withdrawal criteria	9	2	3
Lost to follow-up	1	2	1
Subject participation withdrawn - by investigator	1	1	-
Subject withdrew consent to participate	10	3	9
Protocol deviation	2	-	1
Lack of efficacy	1	2	4

Baseline characteristics

Reporting groups

Reporting group title	Brexpiprazole + Antidepressant therapy (ADT)
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Reporting group description:

Subjects received orally brexpiprazole 1 mg tablet per day and assigned ADT at randomization, and then the dose was increased to 2 mg/day at Day 7 (\pm 2 days). Subjects remained at the target dose (2 mg/day) unless the investigator requested an increase to a higher dose. Change in the dose was done based on a clinical assessment of the benefit and the subject's tolerance of the investigational medicinal product (IMP). The choice of ADT was determined by considering each subject's antidepressant treatment history.

Reporting group title	Quetiapine (Seroquel) extended release (XR) + ADT
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Reporting group description:

Randomized subjects received orally quetiapine XR tablets at a dose of 50 mg/day and assigned ADT therapy on Day 1 and Day 2, and then the dose was increased to 150 mg/day on Day 3 through Day 14. Subjects remained at the target dose (150 mg/day) unless the investigator requested an increase to a higher dose.

Reporting group title	Placebo + ADT
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Reporting group description:

Randomized subjects received orally brexpiprazole or quetiapine matching placebo tablets with the open-label ADT (Phase A) at the final dose reached during the prospective treatment phase.

Reporting group values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT
Number of subjects	197	100	206
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)	197	100	206
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.6	44.6	41.8
standard deviation	\pm 11.5	\pm 11.6	\pm 11.7
Gender categorical Units: Subjects			
Female	128	66	149
Male	69	34	57

Reporting group values	Total		
Number of subjects	503		

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)	503		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	343		
Male	160		

End points

End points reporting groups

Reporting group title	Brexpiprazole + Antidepressant therapy (ADT)
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Reporting group description:

Subjects received orally brexpiprazole 1 mg tablet per day and assigned ADT at randomization, and then the dose was increased to 2 mg/day at Day 7 (\pm 2 days). Subjects remained at the target dose (2 mg/day) unless the investigator requested an increase to a higher dose. Change in the dose was done based on a clinical assessment of the benefit and the subject's tolerance of the investigational medicinal product (IMP). The choice of ADT was determined by considering each subject's antidepressant treatment history.

Reporting group title	Quetiapine (Seroquel) extended release (XR) + ADT
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Reporting group description:

Randomized subjects received orally quetiapine XR tablets at a dose of 50 mg/day and assigned ADT therapy on Day 1 and Day 2, and then the dose was increased to 150 mg/day on Day 3 through Day 14. Subjects remained at the target dose (150 mg/day) unless the investigator requested an increase to a higher dose.

Reporting group title	Placebo + ADT
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Reporting group description:

Randomized subjects received orally brexpiprazole or quetiapine matching placebo tablets with the open-label ADT (Phase A) at the final dose reached during the prospective treatment phase.

Primary: Mean Change From Randomization (End of Phase A) to End of Phase B in montgomery asberg depression rating scale (MADRS) Total Score - Efficacy Sample

End point title	Mean Change From Randomization (End of Phase A) to End of Phase B in montgomery asberg depression rating scale (MADRS) Total Score - Efficacy Sample
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End point description:

To determine the efficacy of brexpiprazole (flexible dose) with placebo as adjunctive therapy by assessment of MADRS total score. The MADRS was used to assess the subject's level of depression by utilizing the structured interview guide for the MADRS (SIGMA). The MADRS consisted of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts) each with 7 defined grades of severity. If a subject discontinued early, every effort was made to complete the "End of Week 18/ET" evaluations.

End point type	Primary
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End point timeframe:

Treatment phase: From Week 8/10 Visit to Week 18/ early termination (ET) Visit

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Number				
least squares mean (standard error)	-6.04 (\pm 0.43)	-4.86 (\pm 0.57)	-4.57 (\pm 0.41)	

Statistical analyses

Statistical analysis title	Bbrexpiprazole+ADT Vs Placebo+ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Placebo + ADT v Brexpiprazole + Antidepressant therapy (ADT)
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	-0.39

Statistical analysis title	Seroquel XR+ADT Vs Placebo+ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6642
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	1.04

Secondary: Mean change from randomization (End of Phase A) to end of Phase B in Sheehan Disability Scale (SDS) score

End point title	Mean change from randomization (End of Phase A) to end of Phase B in Sheehan Disability Scale (SDS) score
End point description:	
The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. It was a visual analogue scale which used spatio-visual, numeric, and verbal descriptive anchors to assess disability across 3 domains and the symptom was marked along the line from 0 (not at all) to 10 (extreme). Scores of 5 and above was associated with significant functional impairment. Additionally, SDS included 2 questions related to productivity losses due to the psychiatric symptoms and impairment.	
End point type	Secondary
End point timeframe:	
Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit	

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Number				
least squares mean (standard error)	-0.97 (± 0.12)	-0.32 (± 0.16)	-0.74 (± 0.11)	

Statistical analyses

Statistical analysis title	Brexpiprazole +ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1334
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.07

Statistical analysis title	Quetiapine +ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	

Comparison groups	Placebo + ADT v Quetiapine (Seroquel) extended release (XR) + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0237
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.78

Secondary: Mean Change From Randomization (End of Phase A) to Phase B by Trial Week in MADRS Total Score at Week 2 visit and Week 4 visit

End point title	Mean Change From Randomization (End of Phase A) to Phase B by Trial Week in MADRS Total Score at Week 2 visit and Week 4 visit
End point description:	
To determine the efficacy of brexpiprazole (flexible dose) with placebo as adjunctive therapy by assessment of MADRS total score. The MADRS was used to assess the subject's level of depression by utilizing the structured interview guide for the MADRS (SIGMA). The MADRS consisted of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts) each with 7 defined grades of severity. If a subject discontinued early, every effort was made to complete the "End of Week 18/ET" evaluations.	
End point type	Secondary
End point timeframe:	
Treatment Phase: At Week 2 visit and Week 4 visit	

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Number				
least squares mean (standard error)				
Week 2 visit (N = 188, 99, 203)	-2.57 (± 0.32)	-2.26 (± 0.41)	-1.04 (± 0.31)	
Week 4 visit (N = 178, 94, 192)	-4.39 (± 0.39)	-3.30 (± 0.51)	-3.22 (± 0.37)	

Statistical analyses

Statistical analysis title	Week 2 visit: Brexpiprazole+ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	-0.76

Statistical analysis title	Week 2 visit: Quetiapine +ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0103
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	-0.29

Statistical analysis title	Week 4 visit: Brexpiprazole+ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	-0.2

Statistical analysis title	Week 4 visit: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8949
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	1.11

Secondary: Mean Change from End of Phase A to Phase B by Study Week in Clinical Global Impression Severity of Illness (CGI-S) Scale

End point title	Mean Change from End of Phase A to Phase B by Study Week in Clinical Global Impression Severity of Illness (CGI-S) Scale
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End point description:

The severity of illness for each subject was rated using the CGI-S. To perform this assessment, the rater or investigator answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 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 patients.

End point type	Secondary
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End point timeframe:

Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit

End point values	Brexiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Number				
least squares mean (standard error)				
Week 2 (N = 188, 99, 203)	-0.26 (± 0.04)	-0.22 (± 0.05)	-0.15 (± 0.04)	
Week 4 (N = 178, 94, 192)	-0.49 (± 0.05)	-0.36 (± 0.06)	-0.37 (± 0.05)	
Week 6 (N = 178, 87, 194)	-0.70 (± 0.05)	-0.60 (± 0.07)	-0.55 (± 0.05)	

Statistical analyses

Statistical analysis title	Week 2: Brexiprazole +ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Brexiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0369
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	-0.01

Statistical analysis title	Week 2: Quetiapine +ADT Vs Placebo + ADT
Statistical analysis description:	
Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.	
Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2468
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.05

Statistical analysis title	Week 4: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0764
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.01

Statistical analysis title	Week 4: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8258
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.17

Statistical analysis title	Week 6: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.01

Statistical analysis title	Week 6: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5601
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.12

Secondary: Mean Clinical Global Impression Improvement Scale (CGI-I) Score by Study Week in Phase B Relative to End of Phase A

End point title	Mean Clinical Global Impression Improvement Scale (CGI-I) Score by Study Week in Phase B Relative to End of Phase A
End point description:	The improvement of each subject's condition was rated for each subject using the CGI-I. The rater or investigator rated the subject's total improvement whether or not it was due entirely to drug treatment. To perform this assessment, the rater or investigator answered the following question: "Compared to his/her condition at baseline, how much has the patient changed?" Response choices include: 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.
End point type	Secondary
End point timeframe:	Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit

End point values	Brexpirazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Mean score arithmetic mean (standard deviation)				
Week 2 (N = 188, 99, 203)	2.94 (± 0.81)	3.01 (± 0.75)	3.10 (± 0.71)	
Week 4 (N = 191, 99, 205)	2.72 (± 0.80)	2.89 (± 0.83)	2.88 (± 0.76)	
Week 6 (N = 191, 99, 205)	2.55 (± 0.84)	2.71 (± 0.87)	2.74 (± 0.83)	

Statistical analyses

Statistical analysis title	Week 2: Brexpirazole+ADT Vs Placebo+ADT
Statistical analysis description:	Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.
Comparison groups	Brexpirazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	-0.03

Statistical analysis title	Week 2: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2053
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.06

Statistical analysis title Week 4: Bbrexpiprazole+ADT Vs Placebo+ADT

Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0222
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.02

Statistical analysis title Week 4: Quetiapine +ADT Vs Placebo + ADT

Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
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Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9403
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.17

Statistical analysis title	Week 6: Bbrexpiprazole+ADT Vs Placebo+ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0146
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.04

Statistical analysis title	Week 6: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7127
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.15

Secondary: MADRS Response Rate (>= 50% reduction in total score) for every trial week visit during double-blind randomized Phase B treatment

End point title	MADRS Response Rate (>= 50% reduction in total score) for every trial week visit during double-blind randomized Phase B treatment
End point description:	The rating was based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allowed a precise rating of severity. The rater decided whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).
End point type	Secondary
End point timeframe:	Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Participants				
week 2 (N = 188, 99, 203)	3	0	3	
Week 4 (N = 191, 99, 205)	8	3	6	
Week 6 (N = 191, 99, 205)	20	8	14	

Statistical analyses

Statistical analysis title	Week 2: Brexpiprazole+ADT Vs Placebo+ADT
Statistical analysis description:	Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.
Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8396
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	6.31

Statistical analysis title	Week 2: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2413
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Week 4: Bbrexpiprazole+ADT Vs Placebo+ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Bbrexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4131
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ration of response rate
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	4.62

Statistical analysis title	Week 4: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
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Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6976
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	5.22

Statistical analysis title	Week 6: Bbrexpiprazole+ADT Vs Placebo+ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2242
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.84

Statistical analysis title	Week 6: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5998
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.98

Secondary: MADRS Remission Rate(<=10 and >=50% reduction in total score) for every trial week visit during double-blind randomized Phase B treatment

End point title	MADRS Remission Rate(<=10 and >=50% reduction in total score) for every trial week visit during double-blind randomized Phase B treatment
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End point description:

The rating was based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allowed a precise rating of severity. The rater decided whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

End point type	Secondary
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End point timeframe:

Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Participants				
Week 2 (N = 188, 99, 203)	1	0	1	
Week 4 (N = 191, 99, 205)	4	0	4	
Week 6 (N = 191, 99, 205)	13	2	9	

Statistical analyses

Statistical analysis title	Week 2: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8711
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	43.6

Statistical analysis title	Week 2: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4795
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Week 4: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8117
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	5.45

Statistical analysis title	Week 4: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
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Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2169
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Week 6: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3321
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.49

Statistical analysis title	Week 6: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3917
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	2.46

Secondary: CGI-I Response rate for every trial week visit during double-blind randomized Phase B treatment

End point title	CGI-I Response rate for every trial week visit during double-blind randomized Phase B treatment
End point description:	The response was defined as a CGI-I score of 1 or 2 (very much improved or much improved). The improvement of each subject's condition was rated for each subject using the CGI-I. The rater or investigator rated the subject's total improvement whether or not it was due entirely to drug treatment. To perform this assessment, the rater or investigator answered the following question: "Compared to his/her condition at baseline, how much has the patient changed?" Response choices include: 1 = very much improved and 2 = much improved.
End point type	Secondary
End point timeframe:	Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	99	205	
Units: Participants				
Week 2 (N = 188, 99, 203)	54	24	35	
Week 4 (N = 191, 99, 205)	78	35	62	
Week 6 (N = 191, 99, 205)	100	48	79	

Statistical analyses

Statistical analysis title	Week 2: Brexpiprazole +ADT Vs Placebo + ADT
Statistical analysis description:	Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.
Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	2.31

Statistical analysis title	Week 2: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1501
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.15

Statistical analysis title Week 4: Brexpiprazole +ADT Vs Placebo + ADT

Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0194
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.74

Statistical analysis title Week 4: Quetiapine +ADT Vs Placebo + ADT

Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Placebo + ADT v Quetiapine (Seroquel) extended release (XR) + ADT
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Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2934
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.63

Statistical analysis title	Week 6: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.66

Statistical analysis title	Week 6: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0898
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of response rate
Point estimate	1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.59

Secondary: The safety and tolerability of brexpiprazole (flexible dose) as adjunctive therapy to ADT in the proposed subject population with major depressive disorder (MDD)

End point title	The safety and tolerability of brexpiprazole (flexible dose) as adjunctive therapy to ADT in the proposed subject population with major depressive disorder (MDD)
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End point description:

Assessment of safety and tolerability included adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including prolactin and glycosylated hemoglobin (HbA1c)], and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference were also measured.

End point type	Secondary
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End point timeframe:

At treatment phase (Week 8 or 10 to Week 18/ET visit) and post-treatment follow-up

End point values	Brexpiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	100	206	
Units: Participants				
Death	0	0	0	
Serious treatment emergent AE (TEAE)	0	1	1	
Discontinuation due to TEAE	2	4	1	
Any TEAE	100	58	107	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from End of Phase A to Phase B in SDS scores for all 3 individual item

End point title	Mean Change from End of Phase A to Phase B in SDS scores for all 3 individual item
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End point description:

The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. It was a visual analogue scale which used spatio-visual, numeric, and verbal descriptive anchors to assess disability across 3 domains and the symptom was marked along the line from 0 (not at all) to 10 (extreme). Scores of 5 and above was associated with significant functional impairment. Additionally, SDS included 2 questions related to

productivity losses due to the psychiatric symptoms and impairment.

End point type	Secondary
End point timeframe:	
Treatment phase: From Week 8/10 Visit to Week 18/ ET Visit	

End point values	Brexiprazole + Antidepressant therapy (ADT)	Quetiapine (Seroquel) extended release (XR) + ADT	Placebo + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191 ^[1]	99 ^[2]	205 ^[3]	
Units: Mean score				
least squares mean (standard error)				
Work/School (N = 109, 55, 125)	-0.59 (± 0.16)	-0.22 (± 0.21)	-0.74 (± 0.16)	
Social life (N = 178, 87, 194)	-1.03 (± 0.13)	-0.26 (± 0.17)	-0.70 (± 0.12)	
Family life (N = 178, 87, 194)	-1.02 (± 0.13)	-0.34 (± 0.18)	-0.67 (± 0.13)	

Notes:

[1] - For work/school, number of subjects analyzed was 125

[2] - For work/school, number of subjects analyzed was 67

[3] - For work/school, number of subjects analyzed was 136

Statistical analyses

Statistical analysis title	Work/School: Brexiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.56

Statistical analysis title	Work/School: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
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Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	1.02

Statistical analysis title	Social life: Brexpiprazole +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Placebo + ADT v Brexpiprazole + Antidepressant therapy (ADT)
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0436
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.01

Statistical analysis title	Social life: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Placebo + ADT v Quetiapine (Seroquel) extended release (XR) + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.84

Statistical analysis title	Family life: Brexpiprazole +ADT Vs Palcebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Brexpiprazole + Antidepressant therapy (ADT) v Placebo + ADT
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0424
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.01

Statistical analysis title	Family life: Quetiapine +ADT Vs Placebo + ADT
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Statistical analysis description:

Efficacy Sample: All participants in the Safety Sample who had an end of Phase A (i.e., Week 8 or 10) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.

Comparison groups	Quetiapine (Seroquel) extended release (XR) + ADT v Placebo + ADT
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.75

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At treatment phase (Week 8 or 10 to Week 18/ET visit) and post-treatment follow-up

Adverse event reporting additional description:

In the safety sample (who received at least 1 dose of double-blind study drug), all AEs with an onset date on or after the start of double-blind treatment; or if the events was continuous from end of phase A and was worsening serious, study drug related, or resulted in death, discontinuation, interruption or reduction of trial therapy.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	Brexpiprazole + ADT
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Reporting group description:

Subjects received orally brexpiprazole 1 mg tablet per day and assigned ADT at randomization, and then the dose was increased to 2 mg/day at Day 7 (\pm 2 days). Subjects remained at the target dose (2 mg/day) unless the investigator requested an increase to a higher dose. Change in the dose was done based on a clinical assessment of the benefit and the subject's tolerance of the investigational medicinal product (IMP).

Reporting group title	Quetiapine (Seroquel) XR + ADT
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Reporting group description:

Randomized subjects received orally quetiapine XR tablets at a dose of 50 mg/day and assigned ADT therapy on Day 1 and Day 2, and then the dose was increased to 150 mg/day on Day 3 through Day 14. Subjects remained at the target dose (150 mg/day) unless the investigator requested an increase to a higher dose.

Reporting group title	Placebo + ADT
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Reporting group description:

Randomized subjects received orally brexpiprazole or quetiapine matching placebo tablets with the open-label ADT (Phase A) at the final dose reached during the prospective treatment phase.

Serious adverse events	Brexpiprazole + ADT	Quetiapine (Seroquel) XR + ADT	Placebo + ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 197 (0.00%)	1 / 100 (1.00%)	1 / 206 (0.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 100 (1.00%)	0 / 206 (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
Psychiatric disorders			

Panic attack			
subjects affected / exposed	0 / 197 (0.00%)	0 / 100 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 + ADT	Quetiapine (Seroquel) XR + ADT	Placebo + ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 197 (20.30%)	27 / 100 (27.00%)	19 / 206 (9.22%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	12 / 197 (6.09%)	3 / 100 (3.00%)	4 / 206 (1.94%)
occurrences (all)	14	3	4
Headache			
subjects affected / exposed	11 / 197 (5.58%)	1 / 100 (1.00%)	10 / 206 (4.85%)
occurrences (all)	14	1	13
Somnolence			
subjects affected / exposed	11 / 197 (5.58%)	18 / 100 (18.00%)	2 / 206 (0.97%)
occurrences (all)	11	22	2
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 197 (1.02%)	6 / 100 (6.00%)	1 / 206 (0.49%)
occurrences (all)	2	6	1
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	5 / 197 (2.54%)	5 / 100 (5.00%)	2 / 206 (0.97%)
occurrences (all)	5	5	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2014	Amendment 1: Clarified necessary trial procedures, inclusion/exclusions criteria and provided updated contact information. Updated to revise the randomization criteria in the blinded addendum, and to make minor administrative changes to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported