Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults with Schizophrenia.

Summary

EudraCT number	2011-005766-38
Trial protocol	PL RO
Global end of trial date	12 February 2015

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	331-10-232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01668797
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
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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	Interim
Date of interim/final analysis	26 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2015
Global end of trial reached?	Yes
Global end of trial date	12 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of brexpiprazole compared with placebo as maintenance treatment in adults with schizophrenia.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, ICH-GCP and applicable local laws and regulatory requirements. Written informed consent was obtained from all participants (or their guardian or legal representative, as applicable according to local laws). Informed consent was obtained and 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). Participants were asked to sign a separate ICF designed for the purpose of collecting a onetime blood sample for assessment of cytochrome P450 (CYP) 2D6 metabolizer genotype. Participants were informed that they would not be excluded from the treatment trial if they did not wish to participate in the pharmacogenomic assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 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	Colombia: 61
Country: Number of subjects enrolled	Malaysia: 47
Country: Number of subjects enrolled	Puerto Rico: 38
Country: Number of subjects enrolled	Serbia: 78
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	Ukraine: 147
Country: Number of subjects enrolled	United States: 204
Country: Number of subjects enrolled	Romania: 73
Worldwide total number of subjects	666
EEA total number of subjects	73

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)	666
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 753 participants were screened at 49 trial sites.

Pre-assignment

Screening details:

Trial had Phase A (Conversion) (N= 406), Phase B (Oral Stabilization) (N= 464; 346 rolled over from Phase A and 118 entered directly into Phase B) and Phase C (Double-Blind Maintenance) with (N= 202 rolled over from Phase B). Participants were randomized in to Phase C in a 1:1 ratio (brexpiprazole: placebo) to receive treatment for up to 52 weeks.

Period 1

Period 1 title	Phase A and Phase B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase A (Conversion Phase)

Arm description:

The purpose of the open-label conversion phase was 2-fold: 1) to cross-titrate the participants current antipsychotic treatment to brexpiprazole monotherapy over a period of 1 to 4 weeks and 2) to allow washout of prohibited medications in preparation for the stabilization phase.

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:

All participants in the Conversion phase received brexpiprazole 1 mg/day as a starting dose and the dose was adjusted within the range of brexpiprazole 1 to 4 mg/day according to the study physician's judgment.

Arm title	Phase B (Stabilization Phase)

Arm description:

This single-blind stabilization phase was to titrate participants to a dose of brexpiprazole (1 to 4 mg/day) that would maintain stability of psychotic symptoms over 12 consecutive weeks (within a maximum of 36 weeks), while minimizing tolerability issues.

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:

All participants in this stabilization phase were titrated to a dose of brexpiprazole (1 to 4 mg/day) that would maintain stability of psychotic symptoms over 12 consecutive weeks (within a maximum of 36 weeks), while minimizing tolerability issues.

Number of subjects in period 1	Phase A (Conversion Phase)	Phase B (Stabilization Phase)
Started	406	464
Completed	346	202
Not completed	60	262
Physician decision	2	11
Consent withdrawn by subject	16	60
Terminated Study on Interim Analysis	19	86
Adverse Event Without Impending Relapse	8	43
Met withdrawal criteria	3	22
Lost to follow-up	3	16
Protocol deviation	2	3
Lack of efficacy	7	21

Period 2

Period 2 title	Phase C
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The randomized treatments were administered in a double-blind fashion with blocks of randomization numbers assigned to trial centers by the Interactive voice response system (IVRS)/ Interactive web response system (IWRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)

Arm description:

Participants received maintenance treatment daily with brexpiprazole (at the final dose achieved during the stabilization phase) for up to 52 weeks.

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:

Participants received maintenance treatment daily with brexpiprazole (at the final dose achieved during the stabilization phase) for up to 52 weeks.

Arm title	Phase C - Placebo (Double-Blind Maintenance Phase)

Arm description:

Participants received placebo orally once daily for 52 weeks.

Arm type	Experimental

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

Dosage and administration details:

Participants received placebo orally once daily for 52 weeks.

Notes:

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

Justification: Period 1 is not baseline period as it consisted of Phase A and Phase B. Phase A was for conversion from other antipsychotics to oral brexpiprazole and washout of prohibited concomitant medications, if applicable. In addition, Phase B was a single-blind treatment phase to stabilize participants on oral brexpiprazole.

Number of subjects in period 2[2][3]	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)
Started	97	105
Completed	14	9
Not completed	83	96
Physician decision	5	2
Consent withdrawn by subject	3	5
Terminated Study on Interim Analysis	49	38
Adverse Event Without Impending Relapse	4	2
Met withdrawal criteria	3	3
Lost to follow-up	4	6
Lack of Efficacy without AE	11	30
Protocol deviation	2	-
Lack of efficacy	2	10

Notes:

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

Justification: All participants who signed the informed consent for the trial and entered the conversion phase or stabilization phase were included in the subjects enrolled per country table. However, the baseline period (Phase C) are those participants who were randomized to receive at least one dose of double-blind study medication in the maintenance phase.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 346 participants entered Phase B; 346 rolled over from Phase A and 118 new patients entered into Phase B directly.

Baseline characteristics

Reporting groups	
Reporting group title	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Reporting group description:	
Participants received maintenance treatment daily with brexpiprazole (at the final dose achieved during the stabilization phase) for up to 52 weeks.	
Reporting group title	Phase C - Placebo (Double-Blind Maintenance Phase)
Reporting group description:	
Participants received placebo orally once daily for 52 weeks.	

Reporting group values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)	Total
Number of subjects	97	105	202
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)	97	105	202
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	38.8	41.6	
standard deviation	± 10.7	± 10.6	-
Gender categorical			
Units: Subjects			
Female	39	40	79
Male	58	65	123

End points

End points reporting groups

Reporting group title	Phase A (Conversion Phase)
Reporting group description:	
The purpose of the open-label conversion phase was 2-fold: 1) to cross-titrate the participants current antipsychotic treatment to brexpiprazole monotherapy over a period of 1 to 4 weeks and 2) to allow washout of prohibited medications in preparation for the stabilization phase.	
Reporting group title	Phase B (Stabilization Phase)
Reporting group description:	
This single-blind stabilization phase was to titrate participants to a dose of brexpiprazole (1 to 4 mg/day) that would maintain stability of psychotic symptoms over 12 consecutive weeks (within a maximum of 36 weeks), while minimizing tolerability issues.	
Reporting group title	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Reporting group description:	
Participants received maintenance treatment daily with brexpiprazole (at the final dose achieved during the stabilization phase) for up to 52 weeks.	
Reporting group title	Phase C - Placebo (Double-Blind Maintenance Phase)
Reporting group description:	
Participants received placebo orally once daily for 52 weeks.	

Primary: Time From Randomization to Exacerbation of Psychotic Symptoms/Impending Relapse in Phase C.

End point title	Time From Randomization to Exacerbation of Psychotic Symptoms/Impending Relapse in Phase C.
End point description:	
The primary efficacy variable was time to impending relapse from randomization, as assessed by Clinical Global Impression of Improvement (CGI-I) score ≥5, Positive and Negative Syndrome Scale (PANSS) scores for hostility or uncooperativeness ≥5, or ≥20% increase in PANSS Total Score. Impending relapse was defined as meeting any of the following 5 criteria: 1) CGI-I score of ≥ 5 (minimally worse) and increase in individual PANSS items to a score > 4 with an absolute increase of ≥ 2 on that specific item or absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content). OR 2) CGI-I score of 6 or 7 (much or very much worse) OR 3) Hospitalization due to worsening of illness OR 4) Any suicidal behavior or answers of "yes" to Questions 4 or 5 on the suicidal ideation section of the C-SSRS OR 5) Violent or aggressive behavior resulting in clinically significant injury.	
End point type	Primary
End point timeframe:	
From randomization to time of exacerbation of psychotic symptoms/impending relapse - up to 52 weeks	

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Days				
number (not applicable)	169	111		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The total number of exacerbation of psychotic symptoms/impending relapse was estimated using a 1:1 (brexpiprazole: placebo) randomization ratio. For the primary endpoint, a 95% confidence interval for the hazard ratio (brexpiprazole vs. placebo) was provided using the Cox Proportional Hazard model with term of treatment in the model.

Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.156
upper limit	0.548

Notes:

[1] - The log-rank test was based on time to exacerbation of psychotic symptoms/impending relapse.

Secondary: Percentage of Participants Meeting Exacerbation of Psychotic Symptoms/Impending Relapse Criteria in the Double-blind Maintenance Phase

End point title	Percentage of Participants Meeting Exacerbation of Psychotic Symptoms/Impending Relapse Criteria in the Double-blind Maintenance Phase

End point description:

Impending relapse was defined as meeting any of the following 5 criteria: 1) CGI-I score of ≥ 5 (minimally worse) and increase in individual PANSS items to a score > 4 with an absolute increase of ≥ 2 on that specific item or an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual though content) to a score of >4 and an absolute increase of ≥ 4 on the combined 4 PANSS items. OR 2) CGI-I score of 6 or 7 (much or very much worse) OR 3) Hospitalization due to worsening of illness OR 4) Current suicidal behavior as assessed by the C-SSRS (ie, an answer of "yes" to any of the questions on the suicidal behavior section of the C-SSRS 5) Violent or aggressive behavior resulting in clinically significant self-injury to another person, or property damage.

End point type	Secondary

End point timeframe:

Baseline and Week 52/Early Termination

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: percentage of participants				
number (not applicable)	13.54	38.46		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The percentage of participants with impending relapse in treatment groups (Brexpiprazole and placebo) in final analysis for participants meeting at least one of the criteria.

Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Mean Change From Baseline in PANSS Marder Factor Scores: Anxiety/Depression Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Anxiety/Depression Score - MMRM Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The anxiety/depression factor score is the sum of score from the 4 items on the anxiety/depression subscale (range: 4 - best possible outcome to 28 - worst possible outcome).

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	0.19 (± 0.25)	0.66 (± 0.24)		

Week 12 (N= 73, 68)	0.54 (± 0.29)	0.78 (± 0.29)		
Week 24 (N= 50, 36)	0.61 (± 0.28)	0.58 (± 0.32)		
Week 36 (N= 33, 24)	0.46 (± 0.33)	0.71 (± 0.39)		
Week 52 (N= 15, 9)	0.04 (± 0.43)	0.28 (± 0.56)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	0.19

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5466
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.55

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9417
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.87

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6257
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0.76

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7437
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	1.21

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4506
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.28

Other pre-specified: Percentage of Participants Meeting Stability Criteria in Double Blind Maintenance Phase

End point title	Percentage of Participants Meeting Stability Criteria in Double Blind Maintenance Phase

End point description:

Participants were assessed for stability using the following criteria:1) Outpatient status AND 2) Positive and Negative Syndrome Scale (PANSS) Total Score ≤ 70 AND 3) A score of ≤ 4 (moderate) on each of the following PANSS items (possible scores of 1 to 7 for each item): conceptual disorganization, suspiciousness hallucinatory behavior, unusual thought content, AND 4) Clinical Global Impression - Severity of Illness scale(CGI-S) score ≤ 4 (moderately ill) AND 5) No current suicidal behavior as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS), defined as the following: An answer of "no" to each question on the Suicidal Behavior section of the C-SSRS AND an answer of "no" to Questions 4 and 5 on the Suicidal Ideation section of the C-SSRS, if completed, AND 6) No evidence of aggressive or violent behavior resulting in clinically significant self-injury, injury to another person, property damage.

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: percentage of participants				
number (not applicable)				
Week 6 (N= 81, 84)	92.59	86.9		
Week 12 (N= 73, 68)	93.15	86.76		
Week 24 (N= 50, 36)	96	94.44		
Week 36 (N= 33, 24)	93.94	83.33		
Week 52 (N= 15, 9)	86.67	88.89		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2296
Method	Chi-squared

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2051
Method	Chi-squared

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7354
Method	Chi-squared

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1977
Method	Chi-squared

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8734
Method	Chi-squared

Other pre-specified: Mean Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score - MMRM Analysis

End point title	Mean Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score - MMRM Analysis

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	0.79 (± 1.31)	4.09 (± 1.27)		
Week 12 (N= 73, 68)	0.84 (± 1.73)	6.15 (± 1.74)		
Week 24 (N= 50, 36)	-1.88 (± 1.39)	2.89 (± 1.55)		
Week 36 (N= 33, 24)	-2.71 (± 1.48)	3.33 (± 1.7)		
Week 52 (N= 15, 9)	0.61 (± 3.34)	6.92 (± 4.53)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0664
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.82
upper limit	0.23

Statistical analysis title	Statistical analysis at Week 12
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0301
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	-0.52

Statistical analysis title	Statistical analysis at Week 24
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0226
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.86
upper limit	-0.68

Statistical analysis title	Statistical analysis at Week 36
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0086
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	-1.59

Statistical analysis title	Statistical analysis at Week 52
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.1
upper limit	5.46

Statistical analysis title	Statistical analysis at across visits
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.01
upper limit	-1.82

Other pre-specified: Mean Change From Baseline in PANSS Total Score - Last-observation-carried-forward (LOCF) Analysis

End point title	Mean Change From Baseline in PANSS Total Score - Last-observation-carried-forward (LOCF) Analysis

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.51 (± 1.4)	3.56 (± 1.28)		
Week 12	1.55 (± 1.77)	6.6 (± 1.62)		
Week 24	1.58 (± 1.88)	9.17 (± 1.72)		
Week 36	2.49 (± 1.89)	10.51 (± 1.73)		
Week 52	3.25 (± 1.94)	11.2 (± 1.77)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	0.23

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-0.9

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-3.18

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	-3.59

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	-3.41

Other pre-specified: Mean Change From Baseline in PANSS Positive Subscale Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Positive Subscale Score - MMRM Analysis

End point description:

PANSS consisted of three subscales: a total of 30 symptom constructs. For each construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS positive subscale score was the sum of the rating scores for the 7 positive scale items from the PANSS panel. The 7 positive symptom constructs are delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS positive subscale score ranged from 7 (best possible outcome) to 49 (worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				

Week 6 (N= 81, 84)	0.17 (± 0.42)	1.28 (± 0.41)		
Week 12 (N= 73, 68)	-0.06 (± 0.5)	1.81 (± 0.51)		
Week 24 (N= 50, 36)	-0.84 (± 0.46)	0.72 (± 0.51)		
Week 36 (N= 33, 24)	-0.97 (± 0.44)	0.91 (± 0.51)		
Week 52 (N= 15, 9)	-1.21 (± 0.73)	1.5 (± 0.99)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Placebo (Double-Blind Maintenance Phase) v Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0507
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	0

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	-0.5

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0215
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	-0.24

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0053
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	-0.58

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0339
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	-0.22

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	-0.88

Other pre-specified: Mean Change From Baseline in PANSS Positive Subscale Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Positive Subscale Score - LOCF Analysis

End point description:

PANSS consisted of three subscales: a total of 30 symptom constructs. For each construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS positive subscale score was the sum of the rating scores for the 7 positive scale items from the PANSS panel. The 7 positive symptom constructs are delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS positive subscale score ranged from 7 (best possible outcome) to 49 (worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.3 (± 0.49)	1.25 (± 0.45)		
Week 12	0.38 (± 0.59)	2.24 (± 0.54)		
Week 24	0.49 (± 0.64)	3.23 (± 0.59)		
Week 36	0.97 (± 0.63)	3.91 (± 0.58)		
Week 52	0.99 (± 0.64)	4.17 (± 0.59)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1093
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.21

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.25
upper limit	-0.47

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.26
upper limit	-1.22

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	-1.44

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	-1.66

Other pre-specified: Mean Change From Baseline in PANSS Negative Subscale Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Negative Subscale Score - MMRM Analysis

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of

7 (extremely severe symptoms). The PANSS negative subscale score was the sum of the rating scores for the 7 negative scale items from the PANSS panel. The 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS negative subscale score ranged from 7 (best possible outcome) to 49 (worst possible outcome).

End point type	Other pre-specified
End point timeframe:	
Weeks 6, 12, 24, 36 and 52	

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	-0.04 (± 0.37)	0.65 (± 0.35)		
Week 12 (N= 73, 68)	-0.22 (± 0.43)	0.55 (± 0.44)		
Week 24 (N= 50, 36)	-0.78 (± 0.39)	0.18 (± 0.42)		
Week 36 (N= 33, 24)	-1.03 (± 0.47)	0.02 (± 0.53)		
Week 52 (N= 15, 9)	1.3 (± 1.37)	0.87 (± 1.71)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.29

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	0.42

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0939
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	0.16

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1396
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	0.35

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.847
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.14
upper limit	5

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2258
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.3

Other pre-specified: Mean Change From Baseline in PANSS Negative Subscale Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Negative Subscale Score - LOCF Analysis

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS negative subscale score was the sum of the rating scores for the 7 negative scale items from the PANSS panel. The 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS negative subscale score ranged from 7 (best possible outcome) to 49 (worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	-0.12 (± 0.39)	0.63 (± 0.35)		
Week 12	-0.17 (± 0.46)	1.06 (± 0.42)		
Week 24	-0.08 (± 0.49)	1.47 (± 0.44)		
Week 36	-0.14 (± 0.51)	1.44 (± 0.46)		
Week 52	0.39 (± 0.54)	1.63 (± 0.49)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0981
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.14

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0264
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.15

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.69
upper limit	-0.42

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	-0.38

Statistical analysis title	Statistical analysis at Week 52
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0516
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.01

Other pre-specified: Change From Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint - MMRM Analysis

End point title	Change From Baseline in Clinical Global Impression-Severity (CGI-S) Score at Endpoint - MMRM Analysis

End point description:

The severity of illness for each participant was rated using the CGI-S scale. To assess CGI-S, the study physician answered 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 ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants.

End point type	Other pre-specified

End point timeframe:

Weeks 2, 12, 24, 26 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	-0.01 (± 0.09)	0.26 (± 0.09)		
Week 12 (N= 73, 68)	-0.01 (± 0.11)	0.37 (± 0.11)		
Week 24 (N= 50, 36)	-0.16 (± 0.1)	0.21 (± 0.1)		
Week 36 (N= 33, 24)	-0.31 (± 0.11)	0.25 (± 0.12)		
Week 52 (N= 15, 9)	-0.23 (± 0.17)	0.28 (± 0.22)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0279
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.03

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.09

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0105
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.09

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.25

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.06

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.15

Other pre-specified: Change From Baseline in CGI-S Score at Endpoint - LOCF Analysis

End point title	Change From Baseline in CGI-S Score at Endpoint - LOCF Analysis

End point description:

The severity of illness for each participant was rated using the CGI-S scale. To assess CGI-S, the study physician answered 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 ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants.

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	-0.08 (± 0.09)	0.17 (± 0.09)		
Week 12	-0.04 (± 0.11)	0.32 (± 0.1)		
Week 24	-0.03 (± 0.11)	0.47 (± 0.1)		
Week 36	0 (± 0.11)	0.56 (± 0.1)		
Week 52	0.02 (± 0.11)	0.55 (± 0.11)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0284
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.03

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Placebo (Double-Blind Maintenance Phase) v Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.11

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.24

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.3

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.26

Other pre-specified: Clinical Global Impression - Improvement Score (CGI-I) at Endpoint - LOCF Analysis

End point title	Clinical Global Impression - Improvement Score (CGI-I) at Endpoint - LOCF Analysis

End point description:

The rater or investigator would rate the participant's total improvement whether or not it is due entirely to study treatment. During Phase B, responses were compared to the participant's condition at Baseline of Phase B (for participants who entered Phase B directly after screening) or to the End of Phase A visit (for participants who participated in Phase A). During Phase C, responses were compared to the participant's condition at the End of Phase B visit. 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	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
arithmetic mean (standard deviation)				

Week 6	3.68 (± 0.98)	4 (± 1.14)		
Week 12	3.66 (± 1.19)	4.1 (± 1.3)		
Week 24	3.67 (± 1.27)	4.3 (± 1.32)		
Week 36	3.71 (± 1.27)	4.39 (± 1.3)		
Week 52	3.77 (± 1.26)	4.4 (± 1.32)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0387
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.07

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.24

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.3

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.25

Other pre-specified: Mean Change From Baseline in Personal and Social Performance (PSP) Scale Score - MMRM Analysis

End point title	Mean Change From Baseline in Personal and Social Performance (PSP) Scale Score - MMRM Analysis

End point description:

The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. Impairment in each of these domains is rated as absent, mild, manifest, marked, severe, or very severe. These ratings are then converted to a total score based on a 100-point scale using algorithms to identify the appropriate 10-point interval, and the rater's judgment to determine the total score within the 10-point interval. Participants with a PSP total score of 71 to 100 are considered to have mild functional difficulty. Scores of 31 to 70 represent manifest disabilities of various degrees and ratings of 1 to 30 indicate minimal functioning that requires intense support and/or supervision. The PSP score ranges from 0 to 100, with higher scores indicating higher levels of social functioning.

End point type	Other pre-specified

End point timeframe:

Weeks 24 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 24 (N= 50, 36)	18.85 (± 1.51)	17.84 (± 1.82)		
Week 52 (N= 15, 9)	18.63 (± 2.76)	12.55 (± 3.48)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6525
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	5.49

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1677
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	14.87

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2347
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	9.5

Other pre-specified: Mean Change From Baseline in PSP Scale Score - LOCF Analysis

End point title	Mean Change From Baseline in PSP Scale Score - LOCF Analysis

End point description:

The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. Impairment in each of these domains is rated as absent, mild, manifest, marked, severe, or very severe. These ratings are then converted to a total score based on a 100-point scale using algorithms to identify the appropriate 10-point interval, and the rater's judgment to determine the total score within the 10-point interval. Participants with a PSP total score of 71 to 100 are considered to have mild functional difficulty. Scores of 31 to 70 represent manifest disabilities of various degrees and ratings of 1 to 30 indicate minimal functioning that requires intense support and/or supervision. The PSP score ranges from 0 to 100, with higher scores indicating higher levels of social functioning.

End point type	Other pre-specified

End point timeframe: Weeks 24 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	100		
Units: Units on a scale				
least squares mean (standard error)				
Week 24	15.2 (± 1.41)	11.41 (± 1.32)		
Week 52	15.06 (± 1.43)	10.31 (± 1.34)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0285
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	7.17

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0071
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	8.18

Other pre-specified: Mean Change From Baseline in Global Assessment of Functioning (GAF) Scale Score - MMRM Analysis

End point title	Mean Change From Baseline in Global Assessment of Functioning (GAF) Scale Score - MMRM Analysis

End point description:

The GAF is a clinician-rated scale that assesses the participant's psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness using a scale that ranges from 1 to 100 score, where lower values indicate worst outcome. From among 10 descriptive anchors, investigators will choose the anchor which is the most representative of the participant's level of functioning at the time of the assessment and will assign a single score within the point range given for the selected anchor.

End point type	Other pre-specified

End point timeframe:

Weeks 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 12 (N= 73, 68)	1.59 (± 1.27)	-0.03 (± 1.29)		
Week 24 (N= 50, 36)	3.74 (± 1.42)	1.09 (± 1.57)		
Week 36 (N= 33, 24)	4.71 (± 1.5)	0.21 (± 1.67)		
Week 52 (N= 15, 9)	5.72 (± 1.87)	-0.16 (± 2.37)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	4.88

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1756
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	6.54

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0331
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	8.63

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0522
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	11.82

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0281
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	6.92

Other pre-specified: Mean Change From Baseline in GAF Scale Score - LOCF Analysis

End point title	Mean Change From Baseline in GAF Scale Score - LOCF Analysis

End point description:

The GAF is a clinician-rated scale that assesses the participant's psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness using a scale that ranges from 1 to 100 score, where lower values indicate worst outcome. From among 10 descriptive anchors, investigators will choose the anchor which is the most representative of the participant's level of functioning at the time of the assessment and will assign a single score within the point range given for the selected anchor.

End point type	Other pre-specified

End point timeframe:

Weeks 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	102		
Units: Units on a scale				
least squares mean (standard error)				
Week 12	0.44 (± 1.26)	-3.44 (± 1.17)		
Week 24	0.85 (± 1.37)	-4.51 (± 1.27)		
Week 36	0.97 (± 1.35)	-5.84 (± 1.25)		
Week 52	0.55 (± 1.38)	-6.01 (± 1.28)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	6.86

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	8.62

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.61
upper limit	10

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.28
upper limit	9.83

Other pre-specified: Percentage of Participants Who Discontinued Due to All Causes	
End point title	Percentage of Participants Who Discontinued Due to All Causes
End point description:	
Analysis of the percentage of participants who discontinued due to all causes was based on all participants who have been randomized and taken one dose of IMP in the Double-blind Maintenance phase. The trial was completed by sponsor when efficacy was demonstrated at the first pre-specified interim analysis (45 impending relapse events) performed by an independent (unblinded) statistician.	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 52	

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Percentage of participants				
number (not applicable)	34.38	54.81		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Statistical analysis for participants who discontinued due to all causes.	
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Logrank

Other pre-specified: Mean Change From Baseline in PANSS Excited Component (PEC) Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Excited Component (PEC) Score - MMRM Analysis
End point description: The PEC score consisted of five PANSS items: excitement (P4), hostility (P7), tension (G4), uncooperativeness (G8), and poor impulse control (G14). Each of the items were rated on a scale of 1 (absent) to 7 (extreme). The PEC scores ranged from 5 (not present) to 35 (extremely severe).	
End point type	Other pre-specified
End point timeframe: Weeks 6, 12, 24, 36 and 52	

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				

Week 6 (N= 81, 84)	0.32 (± 0.23)	0.74 (± 0.22)		
Week 12 (N= 73, 68)	0.5 (± 0.34)	1.16 (± 0.35)		
Week 24 (N= 50, 36)	-0.06 (± 0.31)	0.45 (± 0.36)		
Week 36 (N= 33, 24)	0.1 (± 0.33)	1.25 (± 0.4)		
Week 52 (N= 15, 9)	-0.04 (± 0.46)	1 (± 0.59)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1577
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	0.17

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1685
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	0.28

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2815
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	0.42

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	-0.12

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1803
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	0.51

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	-0.17

Other pre-specified: Mean Change From Baseline in PEC Score - LOCF Analysis	
End point title	Mean Change From Baseline in PEC Score - LOCF Analysis
End point description:	
The PEC score consisted of five PANSS items: excitement (P4), hostility (P7), tension (G4), uncooperativeness (G8), and poor impulse control (G14). Each of the items were rated on a scale of 1 (absent) to 7 (extreme). The PEC scores ranged from 5 (not present) to 35 (extremely severe).	
End point type	Other pre-specified
End point timeframe:	
Weeks 6, 12, 24, 36 and 52	

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.38 (± 0.27)	0.81 (± 0.25)		
Week 12	0.73 (± 0.36)	1.36 (± 0.33)		
Week 24	0.78 (± 0.42)	1.86 (± 0.38)		
Week 36	0.89 (± 0.41)	2.23 (± 0.38)		
Week 52	0.82 (± 0.41)	2.35 (± 0.38)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1852
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.21

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.21

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0323
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	-0.09

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0071
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

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	-0.56

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Positive Symptoms Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Positive Symptoms Score - MMRM Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The positive factor score is the sum of the 8 components of the positive symptoms scale (range: 8 - best possible outcome to 56 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	-0.1 (± 0.45)	1.24 (± 0.44)		
Week 12 (N= 73, 68)	-0.18 (± 0.58)	1.83 (± 0.58)		
Week 24 (N= 50, 36)	-0.82 (± 0.54)	0.77 (± 0.6)		
Week 36 (N= 33, 24)	-1.35 (± 0.57)	0.93 (± 0.63)		
Week 52 (N= 15, 9)	-1.62 (± 0.83)	1.78 (± 1.05)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0288
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-0.14

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0128
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-0.44

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0462
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	0.03

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.94
upper limit	-0.64

Statistical analysis title	Statistical analysis at Week 52
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.05
upper limit	-0.75

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.97

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Positive Symptoms Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Positive Symptoms Score - LOCF Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The positive factor score is the sum of the 8 components of the positive symptoms scale (range: 8 - best possible outcome to 56 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.05 (± 0.5)	1.13 (± 0.46)		
Week 12	0.1 (± 0.61)	2.03 (± 0.56)		
Week 24	0.25 (± 0.66)	3.08 (± 0.61)		
Week 36	0.6 (± 0.66)	3.69 (± 0.6)		
Week 52	0.58 (± 0.66)	4.02 (± 0.6)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Placebo (Double-Blind Maintenance Phase) v Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0695
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.09

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.38
upper limit	-0.49

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	-1.27

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.63
upper limit	-1.54

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	-1.89

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Negative Symptoms Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Negative Symptoms Score - MMRM Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The negative factor score is the sum of the 7 items of the negative subscale (range: 8 - best possible outcome to 56 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	0.02 (± 0.38)	0.68 (± 0.36)		
Week 12 (N= 73, 68)	-0.01 (± 0.45)	0.8 (± 0.45)		
Week 24 (N= 50, 36)	-0.71 (± 0.4)	0.46 (± 0.43)		
Week 36 (N= 33, 24)	-0.8 (± 0.5)	0.7 (± 0.56)		
Week 52 (N= 15, 9)	1.37 (± 1.39)	1.06 (± 1.77)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1969
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.35

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2007
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	0.43

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0436
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.03

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0444
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	-0.04

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8927
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	5.02

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2154
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.31

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Negative Symptoms Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Negative Symptoms Score - LOCF Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The negative factor score is the sum of the 7 items of the negative subscale (range: 8 - best possible outcome to 56 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	-0.24 (± 0.4)	0.61 (± 0.36)		
Week 12	-0.15 (± 0.48)	1.09 (± 0.43)		
Week 24	-0.09 (± 0.49)	1.5 (± 0.44)		
Week 36	-0.07 (± 0.52)	1.56 (± 0.47)		
Week 52	0.34 (± 0.56)	1.57 (± 0.5)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0707
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	0.07

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0276
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	-0.14

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	-0.45

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.42

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	0.07

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Disorganized Thought Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Disorganized Thought Score - MMRM Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The disorganized thoughts factor score is the sum of score from the 7 items on the disorganized thoughts subscale (range: 7 - best possible outcome to 49 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	-0.18 (± 0.31)	0.32 (± 0.3)		
Week 12 (N= 73, 68)	-0.44 (± 0.38)	0.69 (± 0.39)		
Week 24 (N= 50, 36)	-1.26 (± 0.34)	0.27 (± 0.38)		
Week 36 (N= 33, 24)	-1.31 (± 0.44)	0.17 (± 0.5)		
Week 52 (N= 15, 9)	-0.37 (± 0.99)	-0.3 (± 1.24)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Placebo (Double-Blind Maintenance Phase) v Phase C - Brexpiprazole (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2251
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	0.31

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0368
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	-0.07

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	-0.56

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0293
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-0.15

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9632
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	3.17

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	-0.34

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Disorganized Thought Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Disorganized Thought Score - LOCF Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The disorganized thoughts factor score is the sum of score from the 7 items on the disorganized thoughts subscale (range: 7 - best possible outcome to 49 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	-0.32 (± 0.34)	0.33 (± 0.31)		

Week 12	-0.19 (± 0.41)	1.19 (± 0.38)		
Week 24	-0.29 (± 0.44)	1.76 (± 0.41)		
Week 36	0 (± 0.45)	1.95 (± 0.42)		
Week 52	0.29 (± 0.48)	1.97 (± 0.45)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1062
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	0.14

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	-0.42

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	-1.01

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-0.89

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	-0.56

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Uncontrolled Hostility/Excitement Score - MMRM Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Uncontrolled Hostility/Excitement Score - MMRM Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The uncontrolled hostility/excitement factor score is the sum of score from the 4 items on the uncontrolled hostility/excitement subscale (range: 4 - best possible outcome to 28 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6 (N= 81, 84)	0.19 (± 0.19)	0.55 (± 0.18)		
Week 12 (N= 73, 68)	0.33 (± 0.28)	0.82 (± 0.29)		
Week 24 (N= 50, 36)	-0.26 (± 0.27)	0.81 (± 0.31)		
Week 36 (N= 33, 24)	-0.13 (± 0.29)	0.94 (± 0.34)		
Week 52 (N= 15, 9)	-0.2 (± 0.4)	0.94 (± 0.5)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1465
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.13

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2154
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.29

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2696
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.35

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0179
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	-0.19

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0875
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.46
upper limit	0.18

Statistical analysis title	Statistical analysis at across visits.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	-0.24

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Uncontrolled Hostility/Excitement Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Uncontrolled Hostility/Excitement Score - LOCF Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to

as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The uncontrolled hostility/excitement factor score is the sum of score from the 4 items on the uncontrolled hostility/excitement subscale (range: 4 - best possible outcome to 28 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.32 (± 0.22)	0.65 (± 0.21)		
Week 12	0.52 (± 0.3)	0.94 (± 0.28)		
Week 24	0.5 (± 0.36)	1.31 (± 0.33)		
Week 36	0.57 (± 0.36)	1.63 (± 0.33)		
Week 52	0.49 (± 0.37)	1.75 (± 0.34)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2135
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.19

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2437
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	0.29

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0635
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.05

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0144
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	-0.22

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.39

Other pre-specified: Mean Change From Baseline in PANSS Marder Factor Scores: Anxiety/Depression Score - LOCF Analysis

End point title	Mean Change From Baseline in PANSS Marder Factor Scores: Anxiety/Depression Score - LOCF Analysis

End point description:

Retrospective factor analyses have been performed in recent decades using scores for the 30 individual PANSS items to categorize symptoms into 5 dimensions. Collectively, these dimensions are referred to as the PANSS Marder Factor scores and include positive symptoms score, negative symptoms score, thought score, uncontrolled hostility/excitement, anxiety depression score. The anxiety/depression factor score is the sum of score from the 4 items on the anxiety/depression subscale (range: 4 - best possible outcome to 28 - worst possible outcome).

End point type	Other pre-specified

End point timeframe:

Weeks 6, 12, 24, 36 and 52

End point values	Phase C - Brexpiprazole (Double-Blind Maintenance Phase)	Phase C - Placebo (Double-Blind Maintenance Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
least squares mean (standard error)				
Week 6	0.19 (± 0.27)	0.85 (± 0.25)		
Week 12	0.86 (± 0.32)	1.41 (± 0.3)		
Week 24	1.07 (± 0.32)	1.64 (± 0.3)		
Week 36	1.09 (± 0.32)	1.79 (± 0.3)		
Week 52	1.17 (± 0.31)	1.88 (± 0.29)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 6.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0467
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.06

Statistical analysis title	Statistical analysis at Week 12.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1599
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	0.22

Statistical analysis title	Statistical analysis at Week 24.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1417
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	0.19

Statistical analysis title	Statistical analysis at Week 36.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0724
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.06

Statistical analysis title	Statistical analysis at Week 52.
Comparison groups	Phase C - Brexpiprazole (Double-Blind Maintenance Phase) v Phase C - Placebo (Double-Blind Maintenance Phase)
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0608
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reported from the signing of the informed consent throughout the stabilization and treatment period followed by a follow-up phone call or clinic visit (study physician's discretion) of 30 (+2) days after last dose of study medication.

Adverse event reporting additional description:

AEs were collected for participants who received brexpiprazole in the stabilization phase and for participants were randomized to double-blind treatment (brexpiprazole or placebo) and received at least one dose of double-blind study medication in Double-Blind Maintenance Phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Single Blind Stabilization Phase

Reporting group description:

This single-blind stabilization phase was to titrate participants to a dose of brexpiprazole (1 to 4 mg/day) that would maintain stability of psychotic symptoms over 12 consecutive weeks (within a maximum of 36 weeks), while minimizing tolerability issues.

Reporting group title	Brexpiprazole (Double-blind Maintenance Phase)

Reporting group description:

Participants received maintenance treatment daily with brexpiprazole (at the final dose achieved during the stabilization phase) for up to 52 weeks.

Reporting group title	Placebo (Double-blnd Maintenance Phase)

Reporting group description:

Participants received placebo orally once daily for 52 weeks.

Serious adverse events	Single Blind Stabilization Phase	Brexpiprazole (Double-blind Maintenance Phase)	Placebo (Double-blnd Maintenance Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 464 (7.33%)	3 / 97 (3.09%)	11 / 104 (10.58%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 464 (0.00%)	1 / 97 (1.03%)	0 / 104 (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
Injury, poisoning and procedural complications			
Burns second degree			

subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Gun shot wound			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Radius fracture			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 464 (0.00%)	0 / 97 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 464 (0.00%)	0 / 97 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 464 (0.00%)	0 / 97 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Psychotic disorder			
subjects affected / exposed	3 / 464 (0.65%)	1 / 97 (1.03%)	4 / 104 (3.85%)
occurrences causally related to treatment / all	1 / 3	1 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	22 / 464 (4.74%)	1 / 97 (1.03%)	5 / 104 (4.81%)
occurrences causally related to treatment / all	3 / 23	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, paranoid type			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Suicidal ideation			
subjects affected / exposed	3 / 464 (0.65%)	0 / 97 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			

subjects affected / exposed	1 / 464 (0.22%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	1 / 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	Single Blind Stabilization Phase	Brexpiprazole (Double-blind Maintenance Phase)	Placebo (Double-blnd Maintenance Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 464 (31.90%)	0 / 97 (0.00%)	0 / 104 (0.00%)
Investigations			
Weight increased			
subjects affected / exposed	24 / 464 (5.17%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	27	1	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	42 / 464 (9.05%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	57	1	1
Headache			
subjects affected / exposed	23 / 464 (4.96%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	42	6	12
Psychiatric disorders			
Insomnia			
subjects affected / exposed	56 / 464 (12.07%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	90	9	8
Schizophrenia			
subjects affected / exposed	28 / 464 (6.03%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	7	2	2
Agitation			
subjects affected / exposed	30 / 464 (6.47%)	0 / 97 (0.00%)	0 / 104 (0.00%)
occurrences (all)	42	1	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As the interim analysis results were positive, the trial was completed as it achieved the primary endpoint of a significant delay in time to impending relapse for participants randomized to brexpiprazole when compared to participants in placebo.

Notes: