Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Fixed dose OPC-34712 (4, 2, and 1 mg/day) in the Treatment of Adults With Acute Schizophrenia

Summary

EudraCT number	2011-002513-11
Trial protocol	SK
Global end of trial date	29 January 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	331-10-230

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01393613
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
Public contact	Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2014
Global end of trial reached?	Yes
Global end of trial date	29 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to compare the efficacy of each of 3 fixed doses of brexpiprazole with placebo in the treatment of acute schizophrenia in adults. The secondary objective was to compare the safety and tolerability.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 57
Country: Number of subjects enrolled	Croatia: 38
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Philippines: 11
Country: Number of subjects enrolled	Russian Federation: 266
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United States: 243
Worldwide total number of subjects	674
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	672
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 674 participants from 68 trial sites in 8 countries.

Pre-assignment

Screening details:

Adults with schizophrenia as defined by Diagnostic and Statistical Manual of Mental Health Disorders 4th Edition Text Revision criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI) for schizophrenia and psychotic disorders studies were included.

Period 1

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

Blinding implementation details:

Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial. Access to the treatment codes was to have been restricted to personnel charged with generating and maintaining randomization files, packaging study medication, operating the interactive voice response system (IVRS)/ interactive web response system (IWRS), and reporting serious treatment-emergent adverse event (TEAEs) to regulatory agencies.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole 1 mg

Arm description:

Participants were administered oral brexpiprazole 1 milligram (mg) tablet once daily for 6 weeks.

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

Dosage and administration details:

Brexpiprazole 1 mg tablet once daily for 6 weeks.

Arm title	Brexpiprazole 2 mg

Arm description:

Participants were administered oral brexpiprazole 2 mg tablet once daily for 6 weeks.

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

Dosage and administration details:

Brexpiprazole 2 mg tablet once daily for 6 weeks.

Arm title	Brexpiprazole 4 mg

Arm description:

Participants were administered oral brexpiprazole 4 mg tablet once daily for 6 weeks.

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

Dosage and administration details:

Brexpiprazole 4 mg tablet once daily for 6 weeks.

Arm title	Placebo

Arm description:

Participants were administered oral placebo tablet once daily for 6 weeks.

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

Dosage and administration details:

Placebo tablet once daily for 6 weeks.

Number of subjects in period 1	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg
Started	120	186	184
Completed	81	129	130
Not completed	39	57	54
Physician decision	2	-	-
Consent withdrawn by subject	15	25	23
Met withdrawal criteria	-	-	2
Adverse event	11	11	13
Protocol deviation	2	1	-
Lack of efficacy	9	20	16

Number of subjects in period 1	Placebo
Started	184
Completed	118
Not completed	66
Physician decision	1
Consent withdrawn by subject	21
Met withdrawal criteria	1
Adverse event	22
Protocol deviation	-
Lack of efficacy	21

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole 1 mg
Reporting group description:	
Participants were administered oral brexpiprazole 1 milligram (mg) tablet once daily for 6 weeks.	
Reporting group title	Brexpiprazole 2 mg
Reporting group description:	
Participants were administered oral brexpiprazole 2 mg tablet once daily for 6 weeks.	
Reporting group title	Brexpiprazole 4 mg
Reporting group description:	
Participants were administered oral brexpiprazole 4 mg tablet once daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants were administered oral placebo tablet once daily for 6 weeks.	

Reporting group values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg
Number of subjects	120	186	184
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)	119	185	184
From 65-84 years	1	1	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39.1	36.9	38.6
standard deviation	± 11.9	± 10.9	± 11
Gender categorical Units: Subjects			
Female	43	64	71
Male	77	122	113

Reporting group values	Placebo	Total	
Number of subjects	184	674	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	184	672	
From 65-84 years	0	2	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	39.3		
standard deviation	± 10.8	-	
Gender categorical			
Units: Subjects			
Female	73	251	
Male	111	423	

End points

End points reporting groups

Reporting group title	Brexpiprazole 1 mg
Reporting group description:	
Participants were administered oral brexpiprazole 1 milligram (mg) tablet once daily for 6 weeks.	
Reporting group title	Brexpiprazole 2 mg
Reporting group description:	
Participants were administered oral brexpiprazole 2 mg tablet once daily for 6 weeks.	
Reporting group title	Brexpiprazole 4 mg
Reporting group description:	
Participants were administered oral brexpiprazole 4 mg tablet once daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants were administered oral placebo tablet once daily for 6 weeks.	

Primary: Mean change from Baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score.

End point title	Mean change from Baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score.
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). Efficacy sample consisted of all participants who received at least one dose of study medication and had Baseline and at least one Post-Baseline efficacy evaluation.	
End point type	Primary
End point timeframe:	
Baseline to Week 6	

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-16.9 (± 1.86)	-16.61 (± 1.49)	-20 (± 1.48)	-13.53 (± 1.52)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Difference between the average effect of brexpiprazole 2 and 4 mg/day and placebo was tested first at alpha level of 0.05. If statistically significant, then comparisons for each group (brexpiprazole 2 and 4

mg/day) versus placebo were performed at a significance level of 0.05. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0093
Method	Mixed models analysis

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

The primary statistical analysis was to compare brexpiprazole 1mg/day and placebo performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 1 mg
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1588
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.06
upper limit	1.32

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

The primary statistical analysis was to compare brexpiprazole 2mg/day and placebo performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 2 mg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1448
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	1.07

Statistical analysis title	Statistical analysis 4 at Week 6

Statistical analysis description:

The primary statistical analysis was to compare brexpiprazole 2mg/day and placebo performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-2.35

Secondary: Mean change from Baseline to Week 6 in Clinical Global Impression-Severity of Illness Scale (CGI-S) Score.

End point title	Mean change from Baseline to Week 6 in Clinical Global Impression-Severity of Illness Scale (CGI-S) Score.

End point description:

This is the key secondary endpoint. The severity of illness for each participant was rated using the CGI-S. To perform this assessment, 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 at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	120	180	183	181
Units: Units on a scale				
least squares mean (standard error)	-0.91 (± 0.11)	-0.99 (± 0.09)	-1.19 (± 0.08)	-0.81 (± 0.09)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Statistical analysis to compare the average effect analysis for brexpiprazole 2 mg/day and 4 mg/day combined treatment groups at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo v Brexpiprazole 2 mg
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Mixed models analysis

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 1 mg
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4449
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.16

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 2 mg
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1269
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.05

Statistical analysis title	Statistical analysis 4 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.15

Secondary: Mean change from Baseline to Week 6 in Personal and Social Performance (PSP) Score.

End point title	Mean change from Baseline to Week 6 in Personal and Social Performance (PSP) Score.

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 was rated as absent, mild, manifest, marked, severe, or very severe. These ratings were 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 were considered to have mild functional difficulty. Scores of 31 to 70 represented manifest disabilities of various degrees and ratings of 1 to 30 indicated minimal functioning that required intense support and/or supervision. All participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	170	174	163
Units: Units on a scale				
least squares mean (standard error)	11.73 (± 1.19)	10.52 (± 0.95)	13.11 (± 0.94)	8.52 (± 0.97)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0332
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	6.16

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1286
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	4.59

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. MMRM analysis fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	7.17

Secondary: Mean change from Baseline to Week 6 in PANSS Positive Subscale score.

End point title	Mean change from Baseline to Week 6 in PANSS Positive Subscale score.

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 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). Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-5.63 (± 0.62)	-5.42 (± 0.5)	-6.65 (± 0.5)	-4.95 (± 0.51)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3938
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.89

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

The primary statistical analysis was to compare brexpiprazole 2mg/day and placebo performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5101
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	0.93

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0166
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	-0.31

Secondary: Mean change from Baseline to Week 6 in PANSS Negative Subscale score.

End point title	Mean change from Baseline to Week 6 in PANSS Negative Subscale score.

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). Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	130	128	119
Units: Units on a scale				
least squares mean (standard error)	-2.92 (± 0.48)	-2.91 (± 0.38)	-3.36 (± 0.38)	-2.14 (± 0.39)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	0.42

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1547
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	0.29

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0231
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	-0.17

Secondary: Mean Clinical Global Impression-Improvement (CGI-I) Scale Score at Week 6.

End point title	Mean Clinical Global Impression-Improvement (CGI-I) Scale Score at Week 6.

End point description:

The efficacy of trial medication was rated for each participant using the CGI-I. The study physician would rate the participant's total improvement whether or not it is due entirely to drug treatment. All responses were compared to the participant's condition at Baseline prior to the first dose of double-blind study medication. Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	120	180	183	181
Units: Units on a scale				
arithmetic mean (standard deviation)	3.2 (± 1.45)	3.17 (± 1.34)	2.95 (± 1.33)	3.48 (± 1.46)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. Last observation carried forward (LOCF) dataset was to include data recorded at a scheduled visit, ie, all observed cases (OC) data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1358 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.08

Notes:

[1] - CMH row mean scores differ test controlling for study center.

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. LOCF dataset was to include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0422 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.01

Notes:

[2] - CMH row mean scores differ test controlling for study center.

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. LOCF dataset was to include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.2

Notes:

[3] - CMH row mean scores differ test controlling for study center.

Secondary: Percentage of participants with response at Week 6.	
End point title	Percentage of participants with response at Week 6.
End point description:	
The response rate was defined as reduction of ≥30% from Baseline in PANSS Total Score or CGI-I score of 1 or 2. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.	
End point type	Secondary
End point timeframe:	
Week 6	

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: percentage of participants				
number (not applicable)	43.6	38.5	49.7	31.7

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6
Statistical analysis description:	
Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. LOCF dataset was to include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.	
Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0433 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.79

Notes:

[4] - CMH row mean scores differ test controlling for study center.

Statistical analysis title	Statistical analysis 2 at week 6
Statistical analysis description:	
Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. LOCF dataset was to include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.	
Comparison groups	Brexpiprazole 2 mg v Placebo

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.62

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. LOCF dataset was to include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data were not be carried forward to impute missing values for the LOCF dataset.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2

Notes:

[5] - CMH row mean scores differ test controlling for study center.

Secondary: Percentage of participants with discontinuation rate for lack of efficacy at Week 6.

End point title	Percentage of participants with discontinuation rate for lack of efficacy at Week 6.

End point description:

Participants discontinued for lack of efficacy during the trial were reported here. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: percentage of participants				
number (not applicable)	7.69	11.2	8.84	11.7

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6
Statistical analysis description:	
Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6.	
Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4586 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.59

Notes:

[6] - CMH row mean scores differ test controlling for study center.

Statistical analysis title	Statistical analysis 2 at week 6
Statistical analysis description:	
Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6.	
Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9894 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.85

Notes:

[7] - CMH row mean scores differ test controlling for study center.

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:	
Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6.	
Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5202 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.51

Notes:

[8] - CMH row mean scores differ test controlling for study center.

Secondary: Mean change from Baseline to Week 6 in PANSS Excited Component (PEC) Score.

End point title	Mean change from Baseline to Week 6 in PANSS Excited Component (PEC) Score.

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). Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-1.94 (± 0.41)	-1.9 (± 0.33)	-2.86 (± 0.33)	-1.47 (± 0.34)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 1 mg

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3646
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	0.56

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3559
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.48

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.48

Secondary: Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Positive Symptoms Score.

End point title	Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Positive Symptoms Score.

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 (range: 8 to 56): sum of select scores from positive, negative, and general psychopathology subscales. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-6.56 (± 0.66)	-6.26 (± 0.53)	-7.05 (± 0.53)	-5.91 (± 0.54)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4423
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	1.01

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	1.12

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1273
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	0.33

Secondary: Mean change from Baseline to Week 6 in PANSS Marder Factor Scores:

Negative Symptoms Score.	
End point title	Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Negative Symptoms Score.

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 (range: 7 to 49): sum of select scores from negative and general psychopathology subscales. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-3.55 (± 0.48)	-3.53 (± 0.39)	-3.84 (± 0.39)	-2.55 (± 0.4)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	0.22

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction

as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0754
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	0.1

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0194
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.36
upper limit	-0.21

Secondary: Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Disorganized Thought Score.

End point title	Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Disorganized Thought Score.

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 (range: 7 to 49): sum of select scores from positive, negative, and general psychopathology subscales. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-3.46 (± 0.43)	-2.94 (± 0.35)	-3.98 (± 0.34)	-2.59 (± 0.35)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 1 mg
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	0.21

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4753
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	0.61

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	-0.43

Secondary: Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Uncontrolled Hostility and Excitement Score.

End point title	Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Uncontrolled Hostility and Excitement Score.

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 (range: 4 to 28): sum of select scores from positive and general psychopathology subscales. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	130	128	119
Units: Units on a scale				
least squares mean (standard error)	-0.9 (± 0.36)	-0.81 (± 0.29)	-1.89 (± 0.29)	-0.64 (± 0.3)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5752
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.65

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 2 mg
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6792
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.63

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	-0.46

Secondary: Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Anxiety and Depression Score.

End point title	Mean change from Baseline to Week 6 in PANSS Marder Factor Scores: Anxiety and Depression Score.

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 (range: 4 to 28): sum of select scores from general psychopathology subscale. Efficacy sample consisted of all participants who received at least one dose of study medication and have Baseline and at least one Post-Baseline efficacy evaluation.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	179	181	180
Units: Units on a scale				
least squares mean (standard error)	-3.57 (± 0.3)	-3.62 (± 0.24)	-3.78 (± 0.24)	-2.93 (± 0.24)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 1mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 1 mg v Placebo
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	0.1

Statistical analysis title	Statistical analysis 2 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 2mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 2 mg v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0373
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	-0.04

Statistical analysis title	Statistical analysis 3 at week 6

Statistical analysis description:

Statistical analysis to compare brexpiprazole 4mg/day and placebo was performed at Week 6. With fixed effect of treatment, clinical visit, treatment visit interaction, Baseline value, and Baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Placebo

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0104
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from signing of the informed consent until follow-up for up to 30 (+2) days after the last dose of study medication.

Adverse event reporting additional description:

A serious adverse event (SAE) was an untoward medical occurrence that resulted in death or required inpatient hospitalization or prolonged hospitalization. An AE was an exacerbation of an existing problem or a new problem experienced by a participant when enrolled in a trial whether or not it was considered drug related by study physician.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Brexpiprazole 1 mg

Reporting group description:

Participants were administered oral brexpiprazole 1 mg tablet once daily for 6 weeks.

Reporting group title	Brexpiprazole 2 mg

Reporting group description:

Participants were administered oral brexpiprazole 2 mg tablet once daily for 6 weeks.

Reporting group title	Brexpiprazole 4 mg

Reporting group description:

Participants were administered oral brexpiprazole 4 mg tablet once daily for 6 weeks.

Reporting group title	Placebo

Reporting group description:

Participants were administered oral placebo tablets once daily for 6 weeks.

Serious adverse events	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 120 (2.50%)	4 / 186 (2.15%)	4 / 184 (2.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 120 (0.00%)	0 / 186 (0.00%)	0 / 184 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			

subjects affected / exposed	0 / 120 (0.00%)	0 / 186 (0.00%)	0 / 184 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	1 / 120 (0.83%)	0 / 186 (0.00%)	0 / 184 (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	1 / 120 (0.83%)	2 / 186 (1.08%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 120 (0.83%)	2 / 186 (1.08%)	3 / 184 (1.63%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 120 (0.00%)	0 / 186 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 184 (5.43%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	1 / 184 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			

subjects affected / exposed	1 / 184 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	0 / 184 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 184 (0.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	8 / 184 (4.35%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 184 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Brexpiprazole 1 mg	Brexpiprazole 2 mg	Brexpiprazole 4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 120 (30.83%)	65 / 186 (34.95%)	66 / 184 (35.87%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	5 / 120 (4.17%)	9 / 186 (4.84%)	12 / 184 (6.52%)
occurrences (all)	8	10	14
Headache			
subjects affected / exposed	9 / 120 (7.50%)	20 / 186 (10.75%)	19 / 184 (10.33%)
occurrences (all)	12	27	20
Gastrointestinal disorders			

Dyspepsia			
subjects affected / exposed	7 / 120 (5.83%)	7 / 186 (3.76%)	6 / 184 (3.26%)
occurrences (all)	9	8	8
Psychiatric disorders			
Agitation			
subjects affected / exposed	10 / 120 (8.33%)	16 / 186 (8.60%)	13 / 184 (7.07%)
occurrences (all)	11	29	17
Insomnia			
subjects affected / exposed	15 / 120 (12.50%)	25 / 186 (13.44%)	28 / 184 (15.22%)
occurrences (all)	18	32	44
Schizophrenia			
subjects affected / exposed	4 / 120 (3.33%)	6 / 186 (3.23%)	7 / 184 (3.80%)
occurrences (all)	4	6	7

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 184 (38.59%)		
Nervous system disorders			
Akathisia			
subjects affected / exposed	13 / 184 (7.07%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	27 / 184 (14.67%)		
occurrences (all)	40		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	6 / 184 (3.26%)		
occurrences (all)	6		
Psychiatric disorders			
Agitation			
subjects affected / exposed	13 / 184 (7.07%)		
occurrences (all)	22		
Insomnia			
subjects affected / exposed	27 / 184 (14.67%)		
occurrences (all)	44		
Schizophrenia			

subjects affected / exposed occurrences (all)	10 / 184 (5.43%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2012	A formal amendment to the original protocol was to change the primary method for statistical analysis from an analysis of covariance (ANCOVA) model based on the last observation carried forward (LOCF) to MMRM and to add additional clarity to some trial procedures. Clarify that every effort was made to complete efficacy scales prior to administering rescue medication at the last trial (or early termination) visit and that efficacy scales were not done if a new antipsychotic was given before the scales were completed. Add change from Baseline in PANSS Excited Component and PANSS Marder Factor scores as secondary efficacy variables. Clarify that participants who were sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) were not required to use two different methods of birth control and add "other approved birth control device" to the list of acceptable birth control methods. Clarify instructions for preparation of whole blood sample for metabolic profiling. Clarify that participants may remain on stable doses of propranolol during the trial if the propranolol is being taken for an indication other than akathisia. Revise Appendix 9 to include the correct version of the PANSS (ie, 2006). The 2006 version of the PANSS was the version that was distributed to the sites at the start of the trial and was used by raters throughout the trial. In addition, administrative changes were made and typographical errors identified during review of the protocol amendment were corrected.
20 December 2013	A second formal amendment to the original protocol was done to change the primary and secondary efficacy analysis used the Hochberg procedure to control multiplicity. This testing scheme was replaced by the Average Method to be carried out in 2 steps to control the family-wise error rate. In addition, administrative changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported