Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Three Fixed Doses of OPC-34712 in the Treatment of Adults With Acute Schizophrenia

Summary

EudraCT number	2011-002538-38
Trial protocol	LV PL
Global end of trial date	05 December 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	331-10-231

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396421
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
Scientific contact	Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2013
Global end of trial reached?	Yes
Global end of trial date	05 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy, safety and tolerability of each of three fixed doses of OPC-34712 with placebo in the treatment of acute schizophrenia in adults.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and 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	09 August 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	Canada: 7
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 15
Country: Number of subjects enrolled	Latvia: 31
Country: Number of subjects enrolled	Malaysia: 21
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Romania: 109
Country: Number of subjects enrolled	Serbia: 75
Country: Number of subjects enrolled	Ukraine: 115
Country: Number of subjects enrolled	United States: 228
Worldwide total number of subjects	636
EEA total number of subjects	156

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)	634
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 636 participants from 65 trial sites in 10 countries.

Pre-assignment

Screening details:

Participants entered a pre-treatment screening phase of up to 14 days before enrollment to assess eligibility criteria and to washout from prior antipsychotic medications and other prohibited concomitant medications, followed by a 6-week double blinded treatment phase.

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 4 mg

Arm description:

Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

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 4mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

Arm title	Brexpiprazole 2mg

Arm description:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

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 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of

brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

Arm title	Brexpiprazole 0.25mg
Arm description:	
Brexpiprazole 0.25mg 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 0.25mg tablet once daily for 6 weeks.	
Arm title	Placebo
Arm description:	
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 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg
Started	180	182	90
Completed	121	124	56
Not completed	59	58	34
Physician decision	1	1	-
Consent withdrawn by subject	31	24	13
Adverse event	17	15	12
Lost to follow-up	-	-	-
Participant met withdrawal criteria	1	-	1
Protocol deviation	2	1	1
Lack of efficacy	7	17	7

Number of subjects in period 1	Placebo
Started	184
Completed	109
Not completed	75

Physician decision	3
Consent withdrawn by subject	21
Adverse event	32
Lost to follow-up	1
Participant met withdrawal criteria	-
Protocol deviation	-
Lack of efficacy	18

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole 4 mg
Reporting group description:	
Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).	
Reporting group title	Brexpiprazole 2mg
Reporting group description:	
Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.	
Reporting group title	Brexpiprazole 0.25mg
Reporting group description:	
Brexpiprazole 0.25mg tablet once daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet once daily for 6 weeks.	

Reporting group values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg
Number of subjects	180	182	90
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)	180	181	89
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	40.8	39.6	40.5
standard deviation	± 11	± 10.2	± 11.4
Gender categorical			
Units: Subjects			
Female	69	71	29
Male	111	111	61

Reporting group values	Placebo	Total	
Number of subjects	184	636	
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	634	
From 65-84 years	0	2	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	39.7		
standard deviation	± 10.8	-	
Gender categorical			
Units: Subjects			
Female	66	235	
Male	118	401	

End points

End points reporting groups

Reporting group title	Brexpiprazole 4 mg
Reporting group description:	
Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).	
Reporting group title	Brexpiprazole 2mg
Reporting group description:	
Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.	
Reporting group title	Brexpiprazole 0.25mg
Reporting group description:	
Brexpiprazole 0.25mg tablet once daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet once daily for 6 weeks.	

Primary: Mean change from Baseline to Week 6 Positive and Negative Syndrome Scale (PANSS) total score.

End point title	Mean change from Baseline to Week 6 Positive and Negative Syndrome Scale (PANSS) total score.
End point description:	
The PANSS consists of 3 subscales (positive subscale, negative subscale and general psychopathology subscale) containing a total of 30 symptom constructs and was administered using the Structured Clinical Interview (SCI)-PANSS. 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 ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists 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	Primary
End point timeframe:	
Baseline to Week 6	

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-19.65 (± 1.54)	-20.73 (± 1.55)	-14.9 (± 2.23)	-12.01 (± 1.6)

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. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Brexpiprazole 2mg v Placebo
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-8.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-4.4

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-7.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-3.3

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-8.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	-4.37

Statistical analysis title	Statistical analysis 4 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.291
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.27
upper limit	2.49

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 was rated using the CGI-S. To perform this assessment, the rater or 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 participant. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 124, 56 and 109 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	181	89	178
Units: Units on a scale				
least squares mean (standard error)	-1.2 (± 0.08)	-1.15 (± 0.08)	-0.85 (± 0.12)	-0.82 (± 0.09)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

Comparison groups	Brexpiprazole 4 mg v Brexpiprazole 2mg v Placebo
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.15

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, 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	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.15

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.1

Statistical analysis title	Statistical analysis 4 at Week 6

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8491
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.26

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

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

End point description:

The PSP is a clinician-rated scale that measures personal and social functioning in 4 domains: socially useful activities (eg, 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. Efficacy: consists 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 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	173	86	170
Units: Units on a scale				
least squares mean (standard error)	12.72 (± 0.93)	13.15 (± 0.93)	11.84 (± 1.33)	10.26 (± 0.98)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo

Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0557
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	4.98

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	5.42

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3264 [1]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	1.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	4.74

Notes:

[1] - With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, baseline visit interaction as covariates.

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:

For each symptom construct of the PANSS Positive Subscale, 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 symptom constructs were as follows: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	180
Units: Units on a scale				
least squares mean (standard error)	-6.78 (± 0.51)	-6.57 (± 0.52)	-5.46 (± 0.74)	-4.35 (± 0.54)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	-0.99

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.67
upper limit	-0.77

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2227
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.68

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:

For each symptom construct of the PANSS Negative Subscale, 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 symptom constructs were as follows: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-3.65 (± 0.36)	-4.02 (± 0.36)	-3.31 (± 0.53)	-2.24 (± 0.38)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	0.39

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 2mg v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	-0.76

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0996
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	0.2

Secondary: Clinical Global Impression- Improvement scale (CGI-I) score at Week 6

End point title	Clinical Global Impression- Improvement scale (CGI-I) score at Week 6

End point description:

The participant’s overall improvement was rated using the CGI-I. The rater or study physician rated the participant’s total improvement whether or not it was due entirely to drug treatment. All responses were compared with the participant’s condition at screening/baseline. Response choices were: 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 dataset consists 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 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	181	89	178
Units: Units on a scale				
arithmetic mean (standard deviation)	2.94 (± 1.29)	2.94 (± 1.34)	3.37 (± 1.46)	3.48 (± 1.47)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

The same analysis model as described for the primary analysis was applied.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.22

Notes:

[2] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

The same analysis model as described for the primary analysis was applied.

Comparison groups	Placebo v Brexpiprazole 2mg

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.26

Notes:

[3] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

The same analysis model as described for the primary analysis was applied.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4505 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.22

Notes:

[4] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

Secondary: Response rate at Week 6

End point title	Response rate at Week 6

End point description:

Response rate was defined as improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6 or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6. Efficacy dataset consists 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 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Percentage of participants				
number (not applicable)	46.07	47.78	39.08	30.34

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6
Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.91

Notes:

[5] - CMH general association test controlling for trial was applied to the analysis of response rate.

Statistical analysis title	Statistical analysis 2 at Week 6
Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	2.05

Notes:

[6] - CMH general association test controlling for trial was applied to the analysis of response rate.

Statistical analysis title	Statistical analysis 3 at Week 6
Comparison groups	Placebo v Brexpiprazole 0.25mg

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1576 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.76

Notes:

[7] - CMH general association test controlling for trial was applied to the analysis of response rate.

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 consists of 5 PANSS items (excitement [P4], hostility [P7], tension [G4], uncooperativeness [G8], and poor impulse control [G14]). Each rated on a scale of 1 (absent) to 7 (extreme). The PEC for participants was calculated as the sum of the rating assigned to each of the 5 items, and ranged from 5 to 35 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-2.75 (± 0.34)	-2.87 (± 0.34)	-1.99 (± 0.49)	-1.64 (± 0.36)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 0.25mg v Placebo

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5706
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	0.85

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0131
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	-0.26

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0246
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	-0.14

Secondary: Discontinuation rate for lack of efficacy at Week 6

End point title	Discontinuation rate for lack of efficacy at Week 6

End point description:

Discontinuation rate for lack of efficacy during the trial at Week 6 is reported below. Efficacy dataset consists 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 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Percentage of participants				
number (not applicable)	3.93	9.44	8.05	10.11

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6
Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0143 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.85

Notes:

[8] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

Statistical analysis title	Statistical analysis 2 at Week 6
Comparison groups	Placebo v Brexpiprazole 2mg

Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6606 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.65

Notes:

[9] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

Statistical analysis title	Statistical analysis 3 at Week 6
Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5115 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.68

Notes:

[10] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

Secondary: Change from Baseline to Week 6 in PANSS Marder Factor score - Positive Symptoms Score

End point title	Change from Baseline to Week 6 in PANSS Marder Factor score - Positive Symptoms Score

End point description:

The PANSS Marder Factor score - Positive Symptoms Score consists of 8 PANSS items (delusions [P1], hallucinatory behaviour [P3], grandiosity [P5], suspiciousness [P6], stereotyped thinking [N7], somatic concern [G1], unusual thought content [G9], lack of judgment and insight [G10]. Each was rated on a scale of 1 (absent) to 7 (extreme). The PANSS Marder Factor score - Positive Symptoms Score for participants was calculated as the sum of the rating assigned to each of the 8 items, and ranged from 8 to 42 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-7.23 (± 0.51)	-7.37 (± 0.51)	-5.78 (± 0.73)	-4.89 (± 0.53)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.77
upper limit	-0.91

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.91
upper limit	-1.04

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3263
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	0.89

Secondary: Change from Baseline to Week 6 in PANSS Marder Factor score - Negative Symptoms Score

End point title	Change from Baseline to Week 6 in PANSS Marder Factor score - Negative Symptoms Score

End point description:

The PANSS Marder Factor score - Negative Symptoms Score consists of 7 PANSS items (blunted effect [N1], emotional withdrawal [N2], poor rapport [N3], passive/apathetic social withdrawal [N4], lack of spontaneity and conversation flow [N6], motor retardation [G7], active social avoidance [G16]). The PANSS Marder Factor score - Negative Symptoms Score for participants was calculated as the sum of the rating assigned to each of the 7 items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-4.1 (± 0.37)	-4.48 (± 0.37)	-3.66 (± 0.54)	-2.8 (± 0.39)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 4 mg
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0155
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.35
upper limit	-0.25

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-0.62

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1956
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	-0.44

Secondary: Change from Baseline to Week 6 in PANSS Marder Disorganised Thought Score

End point title	Change from Baseline to Week 6 in PANSS Marder Disorganised Thought Score

End point description:

The PANSS Marder Factor score -Disorganized Thought Score consists of 7 PANSS items (conceptual disorganization [P2], difficulty in abstract thinking [N5], mannerisms and posturing [G5], disorientation [G10], poor attention [G11], disturbance of violation [G13], preoccupation [G15]). The PANSS Marder Factor score - Disorganized Thought Score for participants was calculated as the sum of the rating assigned to each of the 7 items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	180
Units: Units on a scale				
least squares mean (standard error)	-3.72 (± 0.36)	-3.94 (± 0.36)	-2.69 (± 0.52)	-1.97 (± 0.37)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	-0.75

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-0.97

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2572
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	0.52

Secondary: Change from Baseline to Week 6 in PANSS Marder Uncontrolled Hostility/Excitement Score

End point title	Change from Baseline to Week 6 in PANSS Marder Uncontrolled Hostility/Excitement Score

End point description:

The PANSS Marder Factor score - Uncontrolled Hostility/Excitement Score consists of 4 PANSS items (excitement [P4], hostility [P7], uncooperativeness [G8], poor impulse control [G14]). The PANSS Marder Factor score - Uncontrolled Hostility/Excitement Score for participants was calculated as the sum of the rating assigned to each of the 4 items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Efficacy: consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brex 4mg, Brex 2mg, Brex 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-1.9 (± 0.28)	-1.91 (± 0.28)	-1.15 (± 0.41)	-0.82 (± 0.3)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	-0.28

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 2mg v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	-0.28

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5172
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	0.66

Secondary: Change from Baseline to Week 6 in PANSS Marder Anxiety Depression Score

End point title	Change from Baseline to Week 6 in PANSS Marder Anxiety Depression Score

End point description:

The PANSS Marder Factor score - Anxiety/Depression Score consists of 4 PANSS items (anxiety [G2], guilt feelings [G3], tension [G4], depression [G6]). The PANSS Marder Factor score - Anxiety/Depression Score for participants was calculated as the sum of the rating assigned to each of the 4 items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Efficacy: consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brex 4mg, Brex 2mg, Brex 0.25 mg and placebo group, respectively had data.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole 4 mg	Brexpiprazole 2mg	Brexpiprazole 0.25mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	178	180	87	178
Units: Units on a scale				
least squares mean (standard error)	-3.4 (± 0.25)	-3.7 (± 0.25)	-3.27 (± 0.35)	-3.05 (± 0.26)

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Brexpiprazole 4 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3284
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.35

Statistical analysis title	Statistical analysis 2 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 2mg
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0655
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.04

Statistical analysis title	Statistical analysis 3 at Week 6

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

Comparison groups	Placebo v Brexpiprazole 0.25mg
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6251
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	0.64

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the participant signs the informed consent form until 30 days after the last dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Brexpiprazole 4mg

Reporting group description:

Brexpiprazole 4mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

Reporting group title	Brexpiprazole 2 mg

Reporting group description:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5-day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

Reporting group title	Brexpiprazole 0.25 mg

Reporting group description:

Brexpiprazole 0.25mg tablet once daily for 6 weeks.

Reporting group title	Placebo

Reporting group description:

Placebo tablet once daily for 6 weeks.

Serious adverse events	Brexpiprazole 4mg	Brexpiprazole 2 mg	Brexpiprazole 0.25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 180 (1.11%)	4 / 182 (2.20%)	4 / 90 (4.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 180 (0.00%)	0 / 182 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 180 (0.00%)	0 / 182 (0.00%)	0 / 90 (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

Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 180 (0.00%)	0 / 182 (0.00%)	0 / 90 (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			
Psychotic disorder			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	2 / 180 (1.11%)	2 / 182 (1.10%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 2	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 180 (0.00%)	0 / 182 (0.00%)	0 / 90 (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
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
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	7 / 184 (3.80%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 184 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Grand mal convulsion			
subjects affected / exposed	1 / 184 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 184 (0.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	2 / 184 (1.09%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	2 / 184 (1.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Schizophrenia, paranoid type			
subjects affected / exposed	1 / 184 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
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 4mg	Brexpiprazole 2 mg	Brexpiprazole 0.25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 180 (35.56%)	53 / 182 (29.12%)	25 / 90 (27.78%)
Nervous system disorders			

Akathisia			
subjects affected / exposed	13 / 180 (7.22%)	8 / 182 (4.40%)	0 / 90 (0.00%)
occurrences (all)	14	8	0
Headache			
subjects affected / exposed	22 / 180 (12.22%)	17 / 182 (9.34%)	9 / 90 (10.00%)
occurrences (all)	28	18	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 180 (3.89%)	3 / 182 (1.65%)	5 / 90 (5.56%)
occurrences (all)	8	3	5
Nausea			
subjects affected / exposed	6 / 180 (3.33%)	10 / 182 (5.49%)	1 / 90 (1.11%)
occurrences (all)	6	10	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	13 / 180 (7.22%)	11 / 182 (6.04%)	4 / 90 (4.44%)
occurrences (all)	15	15	5
Insomnia			
subjects affected / exposed	15 / 180 (8.33%)	16 / 182 (8.79%)	8 / 90 (8.89%)
occurrences (all)	17	20	10
Schizophrenia			
subjects affected / exposed	10 / 180 (5.56%)	7 / 182 (3.85%)	6 / 90 (6.67%)
occurrences (all)	11	7	8

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 184 (35.33%)		
Nervous system disorders			
Akathisia			
subjects affected / exposed	4 / 184 (2.17%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	15 / 184 (8.15%)		
occurrences (all)	19		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	3 / 184 (1.63%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	8 / 184 (4.35%)		
occurrences (all)	9		
Psychiatric disorders			
Agitation			
subjects affected / exposed	19 / 184 (10.33%)		
occurrences (all)	23		
Insomnia			
subjects affected / exposed	18 / 184 (9.78%)		
occurrences (all)	20		
Schizophrenia			
subjects affected / exposed	18 / 184 (9.78%)		
occurrences (all)	18		

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 done to change the primary efficacy analysis used from an Analysis of Covariance (ANCOVA) model based on the LOCF dataset. The MMRM model was included as a sensitivity analysis. Based on regulatory feedback, the MMRM approach was the primary analysis method, with the ANCOVA LOCF used as the sensitivity analysis. Clarified 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. Clarified that participants may remain on stable doses of propranolol during the trial if the propranolol was being taken for an indication other than akathisia. Updated wording of select standard exclusion criteria for consistency with other protocols in the brexpiprazole clinical program. Clarified instructions for preparation of whole blood sample for metabolic profiling. Clarified 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. Added change from Baseline in PANSS Excited Component and PANSS Marder Factor scores as secondary efficacy variables. Revised 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 has been used by raters throughout the trial. In addition, administrative changes were made and typographical errors identified during review of the protocol amendment were corrected.
05 December 2013	The second formal amendment to the original protocol was to change the statistical method for controlling multiplicity from the Hochberg procedure to the family-wise error rate. The actual protocol amendment was dated 20-Dec-2013 which was after the trial completed but before database lock.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported