Clinical trial results:
A Long-term, Phase 3, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Oral OPC-34712 as Maintenance Treatment in Adults with Schizophrenia

Summary

EudraCT number	2011-002514-37
Trial protocol	LV PL SK
Global end of trial date	25 February 2016

Results information

Result version number	v1 (current)
This version publication date	26 February 2017
First version publication date	26 February 2017

Trial information

Trial identification

Sponsor protocol code	331-10-237

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01397786
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	Otsuka Data Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Data Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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	25 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2016
Global end of trial reached?	Yes
Global end of trial date	25 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of oral brexpiprazole as monotherapy in adults with schizophrenia. This trial was conducted on an outpatient basis.

Protection of trial subjects:

In accordance with the 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. Written informed consent was obtained from all participants. Informed consent was obtained and documented prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s). All participants received copies of their signed and dated ICFs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 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: 3
Country: Number of subjects enrolled	Colombia: 57
Country: Number of subjects enrolled	Croatia: 17
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 9
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Malaysia: 31
Country: Number of subjects enrolled	Mexico: 34
Country: Number of subjects enrolled	Philippines: 6
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Puerto Rico: 14
Country: Number of subjects enrolled	Romania: 80
Country: Number of subjects enrolled	Russian Federation: 121
Country: Number of subjects enrolled	Serbia: 89
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ukraine: 147

Country: Number of subjects enrolled	United States: 432
Country: Number of subjects enrolled	Turkey: 12
Worldwide total number of subjects	1072
EEA total number of subjects	106

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)	1072
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in a total of 1072 participants (1044 of whom entered the open-label treatment phase) at 202 trial sites.

Pre-assignment

Screening details:

Enrollment was drawn from eligible participants who could potentially benefit from monotherapy treatment with oral brexpiprazole for schizophrenia and included rollover participants from the double-blind, phase-3 efficacy trials (ie, Trials 2011-002513-11, 2011-002538-38, and 2011-005766-38) and de novo participants from select sites.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Brexpiprazole

Arm description:

Participants who rolled over from, and received blinded brexpiprazole in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

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

Dosage and administration details:

Participants received oral brexpiprazole 1 to 4mg/day for 4 weeks.

Arm title	Prior Placebo

Arm description:

Participants who rolled over from, and received blinded placebo in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

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

Dosage and administration details:

Participants received oral placebo for 4 weeks.

Arm title	De Novo

Arm description:

Participants who had not previously participated in a brexpiprazole clinical study and who received 1-4

mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

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

Dosage and administration details:

De Novo participants received brexpiprazole 1-4 mg/day for 4 weeks.

Number of subjects in period 1	Prior Brexpiprazole	Prior Placebo	De Novo
Started	611	204	257
Completed	308	109	91
Not completed	303	95	166
Physician decision	9	1	4
Consent withdrawn by subject	102	45	35
Adverse events	109	23	35
Met withdrawal criteria	38	5	45
Lost to follow-up	22	12	28
Protocol deviation	1	2	4
Lack of efficacy	22	7	15

Baseline characteristics

Reporting groups	
Reporting group title	Prior Brexpiprazole
Reporting group description:	
Participants who rolled over from, and received blinded brexpiprazole in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.	
Reporting group title	Prior Placebo
Reporting group description:	
Participants who rolled over from, and received blinded placebo in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.	
Reporting group title	De Novo
Reporting group description:	
Participants who had not previously participated in a brexpiprazole clinical study and who received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.	

Reporting group values	Prior Brexpiprazole	Prior Placebo	De Novo
Number of subjects	611	204	257
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)	611	204	257
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.5	39.6	44.1
standard deviation	± 10.8	± 10.8	± 11.1
Gender categorical Units: Subjects			
Female	245	79	85
Male	366	125	172

Reporting group values	Total		
Number of subjects	1072		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	1072		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	409		
Male	663		

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Participants who rolled over from, and received blinded brexpiprazole in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Reporting group title	Prior Placebo

Reporting group description:

Participants who rolled over from, and received blinded placebo in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Reporting group title	De Novo

Reporting group description:

Participants who had not previously participated in a brexpiprazole clinical study and who received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Subject analysis set title	Total
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who rolled over from, and received blinded brexpiprazole/placebo in, one of the randomized, double blind, placebo controlled Phase 3 efficacy studies (Trials 2011-002513-11, 2011-002538-38, and 2011-005766-38); or de novo patients. All received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Primary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)[1]

End point description:

A treatment-emergent adverse event (TEAE) is defined as an AE that started after start of investigational medicinal product (IMP) treatment; or if the event was continuous from baseline and was serious, IMP-related, or resulted in death, discontinuation, interruption or reduction of IMP. Safety sample included those participants who had at least one post-baseline efficacy evaluation for Positive and Negative Syndrome Scale (PANSS) total score.

End point type	Primary

End point timeframe:

From Baseline up to 52 Weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistical analysis was performed.

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	605	202	224	1031
Units: percentage of participants				
number (not applicable)				
With AEs	60.2	56.4	65.2	60.5
With TEAEs	60	56.4	65.2	60.4
With SAEs	14.9	8.9	11.2	12.9

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Positive and Negative Syndrome Scale Total Score

End point title	Mean Change From Baseline in Positive and Negative Syndrome Scale Total Score

End point description:

The PANSS consisted of three subscales that contained a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 that indicated the absence of symptoms and a score of 7 indicated extremely severe symptoms. The PANSS total score was the sum of the rating scores for 7 positive subscale items, 7 negative subscale items, and 16 general psychopathology subscale items from the PANSS panel. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	223	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-6.9 (± 12.9)	-12.5 (± 14.9)	-6.6 (± 13.6)	-8 (± 13.6)
Mean change at Week 52 (n= 226, 93, 91, 410)	-11 (± 14.4)	-18.4 (± 16.9)	-8.8 (± 12.6)	-12.2 (± 15)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-3.8 (± 16.7)	-9.7 (± 18.7)	-3.5 (± 14.3)	-4.9 (± 16.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Positive Subscale Score

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

End point description:

The PANSS consisted of three subscales that contained a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicated the absence of symptoms and a score of 7 indicated extremely severe symptoms. In positive subscale, the 7 positive symptom constructs were: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-2.1 (± 4.5)	-4.1 (± 5.4)	-1.7 (± 4.3)	-2.4 (± 4.7)
Mean change at Week 52 (n= 226, 93, 91, 410)	-3.2 (± 4.6)	-5.8 (± 5.2)	-2.3 (± 4.1)	-3.6 (± 4.8)
Mean change at Last Visit(n= 591, 198, 223, 1012)	-0.9 (± 5.9)	-2.8 (± 6.4)	-1 (± 4.9)	-1.3 (± 5.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Negative Subscale Score

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

End point description:

The PANSS consisted of three subscales that contained a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated the absence of symptoms and a score of 7 indicated extremely severe symptoms. In negative subscale the severity was rated for the following 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	223	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-1.4 (± 3.7)	-2.4 (± 4.3)	-1.3 (± 3.8)	-1.6 (± 3.9)
Mean change at Week 52 (n= 226, 93, 91, 410)	-2.7 (± 4.5)	-3.7 (± 5.4)	-2 (± 3.7)	-2.8 (± 4.6)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-1 (± 4.1)	-2.4 (± 5)	-0.6 (± 4.2)	-1.2 (± 4.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Clinical Global Impression - Severity of Illness Scale Score

End point title	Mean Change From Baseline in Clinical Global Impression - Severity of Illness Scale Score

End point description:

The severity of illness for each participant were rated using the CGI-S. To perform this assessment, the investigator were to answer the following question: "Considering your total clinical experience with this particular population, how mentally ill was the participant at that time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	223	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-0.35 (± 0.79)	-0.6 (± 0.98)	-0.24 (± 0.88)	-0.38 (± 0.86)
Mean change at Week 52 (n= 226, 93, 91, 410)	-0.55 (± 0.86)	-0.97 (± 0.98)	-0.48 (± 0.86)	-0.63 (± 0.91)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-0.14 (± 1.04)	-0.46 (± 1.12)	-0.17 (± 0.88)	-0.21 (± 1.03)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Personal and Social Performance (PSP) Scale Total Score

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

End point description:

The PSP was a validated clinician-rated scale that measured 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 that determined 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. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 366, 134, 123, 623)	4.5 (± 9.7)	6.5 (± 11.3)	4.5 (± 9)	4.9 (± 10)
Mean change at Week 52 (n= 223, 93, 91, 407)	7 (± 10.6)	9.6 (± 11.9)	7.6 (± 10.8)	7.7 (± 11)
Mean change at Last Visit (n= 569, 196, 219, 984)	1.8 (± 12.4)	5.1 (± 12.8)	2.7 (± 11)	2.7 (± 12.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Clinical Global Impression - Improvement Score

End point title	Mean Clinical Global Impression - Improvement Score

End point description:

The efficacy of study medication was rated for each participant using the CGI-I. The investigator rated the participants total improvement whether or not it was due to the drug treatment. All responses were compared to the participants condition at Screening/Baseline (i.e, Week 6 visit of Protocol NCT00905307). Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	598	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 26 (n= 381, 134, 123, 638)	3 (± 1.13)	2.77 (± 0.99)	3 (± 1.13)	2.95 (± 1.1)
Week 52 (n= 226, 93, 91, 410)	2.66 (± 1.13)	2.26 (± 0.97)	2.76 (± 1.09)	2.59 (± 1.1)
Last Visit (n= 598, 198, 223, 1019)	3.31 (± 1.43)	2.96 (± 1.33)	3.3 (± 1.27)	3.24 (± 1.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate

End point title	Response Rate

End point description:

Response rate was defined as a reduction of ≥ 30% from Baseline in PANSS total score or CGI-I score of 1 (very much improved) or 2 (much improved) at the Last Visit. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	605	202	224	1031
Units: Percentage of participants				
number (not applicable)	34.2	42.6	27.2	34.3

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation Rate for Lack of Efficacy

End point title	Discontinuation Rate for Lack of Efficacy

End point description:

Discontinuation rate for the participants who discontinued due to lack of efficacy were examined. The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	605	202	224	1031
Units: percentage of participants				
number (not applicable)	3.6	3.5	6.3	4.2

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Positive and Negative Syndrome Scale Excited Component Score

End point title	Mean Change From Baseline in Positive and Negative Syndrome Scale Excited Component 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). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-0.6 (± 3.1)	-1.8 (± 3.7)	-0.7 (± 3.1)	-0.9 (± 3.3)
Mean change at Week 52 (n= 226, 93, 91, 410)	-1.2 (± 3.2)	-2.6 (± 3.4)	-1 (± 2.9)	-1.5 (± 3.2)
Mean change at Last Visit (n= 591, 198, 223, 1012)	0.1 (± 4.1)	-0.9 (± 4.2)	-0.3 (± 3.5)	-0.2 (± 4)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Marder Factor Scores - Positive Symptoms Score

End point title	Mean Change From Baseline 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 is the sum of the 8 components of the positive symptoms scale (range: 8 - best possible outcome to 56 - worst possible outcome). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-2.6 (± 4.8)	-4.7 (± 5.5)	-2 (± 5.2)	-2.9 (± 5.1)
Mean change at Week 52 (n= 226, 93, 91, 410)	-3.9 (± 5.2)	-6.6 (± 5.7)	-2.6 (± 4.8)	-4.2 (± 5.4)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-1.6 (± 5.9)	-3.5 (± 6.5)	-1.3 (± 5)	-1.9 (± 5.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Marder Factor Scores - Negative Symptoms Score

End point title	Mean Change From Baseline 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 is the sum of the 7 items of the negative subscale (range: 8 - best possible outcome to 56 - worst possible outcome). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for
PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-1.5 (± 3.6)	-2.2 (± 4)	-1.7 (± 4.1)	-1.7 (± 3.8)
Mean change at Week 52 (n= 226, 93, 91, 410)	-2.6 (± 4.3)	-3.9 (± 5)	-2.2 (± 3.8)	-2.8 (± 4.4)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-1 (± 4.1)	-2.3 (± 5.1)	-0.7 (± 4.1)	-1.2 (± 4.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Marder Factor Scores - Disorganized Thought Score

End point title	Mean Change From Baseline 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 is the sum of score from the 7 items on the disorganized thoughts subscale (range: 7 - best possible outcome to 49 - worst possible outcome). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-1.7 (± 3.3)	-2.6 (± 3.5)	-1.7 (± 3.5)	-1.9 (± 3.4)
Mean change at Week 52 (n= 226, 93, 91, 410)	-2.9 (± 3.7)	-3.7 (± 4.6)	-2.3 (± 3.7)	-2.9 (± 4)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-1.2 (± 4.2)	-2.2 (± 4.5)	-0.9 (± 4)	-1.4 (± 4.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PANSS Marder Factor Scores - Hostility/ Excitement Score

End point title	Mean Change From Baseline in PANSS Marder Factor Scores - Hostility/ 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 is the sum of score from the 4 items on the uncontrolled hostility/excitement subscale (range: 4 - best possible outcome to 28 - worst possible outcome). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-0.4 (± 2.7)	-1.4 (± 3.1)	-0.6 (± 2.6)	-0.6 (± 2.8)
Mean change at Week 52 (n= 226, 93, 91, 410)	-0.8 (± 2.7)	-1.9 (± 2.9)	-0.9 (± 2.3)	-1.1 (± 2.7)
Mean change at Last Visit (n= 591, 198, 223, 1012)	0.2 (± 3.4)	-0.7 (± 3.5)	-0.3 (± 3)	-0.1 (± 3.4)

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean Change From Baseline in PANSS Marder Factor Scores - Anxiety/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 is the sum of score from the 4 items on the anxiety/depression subscale (range: 4 - best possible outcome to 28 - worst possible outcome). The Efficacy Sample included participants in the Safety Sample who had at least 1 post-baseline efficacy evaluation for PANSS Total Score.

End point type	Secondary

End point timeframe:

From Baseline up to 52 Weeks

End point values	Prior Brexpiprazole	Prior Placebo	De Novo	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	591	198	123	1012
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mean change at Week 26 (n= 375, 134, 123, 632)	-0.7 (± 2.6)	-1.5 (± 3)	-0.7 (± 3.4)	-0.9 (± 2.9)
Mean change at Week 52 (n= 226, 93, 91, 410)	-0.9 (± 2.5)	-2.4 (± 2.9)	-0.8 (± 3.5)	-1.2 (± 2.9)
Mean change at Last Visit (n= 591, 198, 223, 1012)	-0.2 (± 3.2)	-0.9 (± 3.4)	-0.4 (± 3.8)	-0.4 (± 3.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The trial required that participants be actively monitored for AEs up to 30 (+2) days after the last dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	De Novo (Phase A)

Reporting group description:

Participants underwent cross-titration to oral brexpiprazole for 4 weeks in Phase A. DeNovo participants in Phase A received brexpiprazole monotherapy starting dose of 2 mg daily at the conversion Week 4 visit (baseline visit of Phase B).

Reporting group title	Prior Brexpiprazole (Phase B)

Reporting group description:

Participants who rolled over from, and received blinded brexpiprazole in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Reporting group title	Prior Placebo (Phase B)

Reporting group description:

Participants who rolled over from, and received blinded placebo in, one of the randomized, double-blind, placebo-controlled Phase 3 efficacy studies (Trials 2011-002513-11; 2011-002538-38; 2011-005766-38); all received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Reporting group title	De Novo (Phase B)

Reporting group description:

Participants who had not previously participated in a brexpiprazole clinical study and who received 1-4 mg of daily treatment with open label brexpiprazole in trial 2011-002514-37.

Serious adverse events	De Novo (Phase A)	Prior Brexpiprazole (Phase B)	Prior Placebo (Phase B)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 226 (1.77%)	90 / 605 (14.88%)	18 / 202 (8.91%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			

subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pneumonia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Rib fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Coronary artery disease			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 226 (0.00%)	2 / 605 (0.33%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrovascular accident			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (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
Seizure			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (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
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Completed suicide			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emotional disorder			
subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (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
Psychotic disorder			
subjects affected / exposed	1 / 226 (0.44%)	7 / 605 (1.16%)	3 / 202 (1.49%)
occurrences causally related to treatment / all	0 / 1	1 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			

subjects affected / exposed	2 / 226 (0.88%)	68 / 605 (11.24%)	12 / 202 (5.94%)
occurrences causally related to treatment / all	0 / 2	26 / 71	5 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia paranoid type			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	1 / 226 (0.44%)	0 / 605 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 226 (0.00%)	2 / 605 (0.33%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 226 (0.00%)	2 / 605 (0.33%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 226 (0.00%)	0 / 605 (0.00%)	0 / 202 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 605 (0.17%)	0 / 202 (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	De Novo (Phase B)		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 256 (9.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine cancer			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Pneumonia			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			

subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			

subjects affected / exposed	2 / 256 (0.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 256 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Emotional disorder				
subjects affected / exposed	0 / 256 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucination, auditory				
subjects affected / exposed	0 / 256 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	4 / 256 (1.56%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	10 / 256 (3.91%)			
occurrences causally related to treatment / all	6 / 14			
deaths causally related to treatment / all	0 / 0			
Schizophrenia paranoid type				
subjects affected / exposed	0 / 256 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal behaviour				
subjects affected / exposed	0 / 256 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				

subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 256 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 256 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 256 (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	De Novo (Phase A)	Prior Brexpiprazole (Phase B)	Prior Placebo (Phase B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 226 (0.00%)	166 / 605 (27.44%)	53 / 202 (26.24%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 226 (0.00%)	47 / 605 (7.77%)	15 / 202 (7.43%)
occurrences (all)	0	53	16
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 226 (0.00%)	10 / 605 (1.65%)	2 / 202 (0.99%)
occurrences (all)	0	10	3
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 226 (0.00%)	22 / 605 (3.64%)	14 / 202 (6.93%)
occurrences (all)	0	25	21
Headache			
subjects affected / exposed	0 / 226 (0.00%)	42 / 605 (6.94%)	14 / 202 (6.93%)
occurrences (all)	0	51	16
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 226 (0.00%)	30 / 605 (4.96%)	7 / 202 (3.47%)
occurrences (all)	0	42	15
Insomnia			
subjects affected / exposed	0 / 226 (0.00%)	51 / 605 (8.43%)	17 / 202 (8.42%)
occurrences (all)	0	71	25

Non-serious adverse events	De Novo (Phase B)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 256 (37.11%)		
Investigations			
Weight increased			
subjects affected / exposed	23 / 256 (8.98%)		
occurrences (all)	25		
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 256 (7.81%)		
occurrences (all)	20		
Nervous system disorders			

Akathisia			
subjects affected / exposed	14 / 256 (5.47%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	24 / 256 (9.38%)		
occurrences (all)	29		
Psychiatric disorders			
Agitation			
subjects affected / exposed	23 / 256 (8.98%)		
occurrences (all)	31		
Insomnia			
subjects affected / exposed	32 / 256 (12.50%)		
occurrences (all)	38		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2012	Inclusion of rollover participants from Trial 2011-005766-38.
19 June 2014	Reduction of trial duration from 52 to 26 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported